A Review of Infertility

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

Faculty

Teisha Phillips, RN, BSN, received her Bachelor of Science in Nursing degree from Point Loma Nazarene University in 2005. She has nursing experience in a variety of clinical settings including multispecialty outpatient surgery, fertility, women's health, and cosmetic/aesthetic nursing. Her primary focus and passion is on direct patient care and patient education. She is presently employed as a perioperative nurse at an outpatient surgery center in the greater Sacramento area.

Faculty Disclosure

Contributing faculty, Teisha Phillips, RN, BSN, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Division Planners

John M. Leonard, MD
Alice Yick Flanagan, PhD, MSW
Sharon Cannon, RN, EdD, ANEF
Margaret Donohue, PhD

Senior Director of Development and Academic Affairs

Sarah Campbell

Division Planners/Director Disclosure

The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for all healthcare professionals, including nurses, primary care physicians, obstetricians, gynecologists, and mental health specialists, involved in the care of patients experiencing either primary or secondary infertility.

Accreditations & Approvals

JOINTLY ACCREDITED PROVIDER™ INTERPROFESSIONAL CONTINUING EDUCATION

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

As a Jointly Accredited Organization, NetCE is approved to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Organizations, not individual courses, are approved under this program. Regulatory boards are the final authority on courses accepted for continuing education credit.

American Psychological Association

Continuing Education (CE) credits for psychologists are provided through the co-sponsorship of the American Psychological Association (APA) Office of Continuing Education in Psychology (CEP). The APA CEP Office maintains responsibility for the content of the programs.

NetCE has been approved by NBCC as an Approved Continuing Education Provider, ACEP No. 6361. Programs that do not qualify for NBCC credit are clearly identified. NetCE is solely responsible for all aspects of the programs.

Designations of Credit

NetCE designates this enduring material for a maximum of 10 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

A complete Works Cited list begins on page 45.

Mention of commercial products does not indicate endorsement.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 10 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the learner to earn credit toward the CME and Self-Assessment requirements of the American Board of Surgery's Continuous Certification program. It is the CME activity provider's responsibility to submit learner completion information to ACCME for the purpose of granting ABS credit.

This activity has been designated for 10 Lifelong Learning (Part II) credits for the American Board of Pathology Continuing Certification Program.

Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

NetCE designates this continuing education activity for 10 ANCC contact hours.

IPCE CREDIT™

This activity was planned by and for the healthcare team, and learners will receive 10 Interprofessional Continuing Education (IPCE) credits for learning and change.

NetCE designates this continuing education activity for 12 hours for Alabama nurses.

NetCE designates this continuing education activity for 1 pharmacotherapeutic/pharmacology contact hour.

AACN Synergy CERP Category A.

Social workers completing this intermediate-to-advanced course receive 10 Clinical continuing education credits.

NetCE designates this continuing education activity for 10 CE credits.

NetCE designates this continuing education activity for 4 NBCC clock hours.

Individual State Nursing Approvals

In addition to states that accept ANCC, NetCE is approved as a provider of continuing education in nursing by: Alabama, Provider #ABNP0353 (valid through 07/29/2025); Arkansas, Provider #50-2405; California, BRN Provider #CEP9784; California, LVN Provider #V10662; California, PT Provider #V10842; District of Columbia, Provider #50-2405; Florida, Provider #50-2405; Georgia, Provider #50-2405; Kentucky, Provider #7-0054 (valid through 12/31/2025); South Carolina, Provider #50-2405; West Virginia, RN and APRN Provider #50-2405.

Individual State Behavioral Health Approvals

In addition to states that accept ASWB, NetCE is approved as a provider of continuing education by the following state boards: Alabama State Board of Social Work Examiners, Provider #0515; Florida Board of Clinical Social Work, Marriage and Family Therapy and Mental Health, Provider #50-2405; Illinois Division of Professional Regulation for Social Workers, License #159.001094; Illinois Division of Professional Regulation for Licensed Professional and Clinical Counselors, License #197.000185; Illinois Division of Professional Regulation for Marriage and Family Therapists, License #168.000190.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

Given that an estimated 10% of couples in the United States are infertile, it is inevitable that many healthcare professionals will encounter patients seeking medical help for this condition. The purpose of this course is to provide healthcare professionals with the information necessary to make a timely and accurate diagnosis of infertility, treatment and referral decisions regarding the infertile patient or couple, and sensitive patient education in order to ensure the highest level of care and patient satisfaction.

Learning Objectives

Upon completion of this course, you should be able to:

1. Identify the two basic types of infertility.
2. Outline the epidemiology of infertility in the United States.
3. Review the anatomy and physiology associated with male and female infertility.
4. Recognize the pathophysiology of male and female infertility.
5. Identify the various risk factors associated with infertility.
6. Compare and evaluate the diagnostic findings associated with infertility.
7. Recommend lifestyle modifications for patients with infertility.
8. Select appropriate pharmacotherapeutic interventions for improving fertility.
9. Evaluate surgical, radiologic, and assisted reproductive technology (ART) interventions, including donor eggs or sperm, induced ovulation, in-vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), and zygote intrafallopian transfer (ZIFT).
10. Evaluate the psychosocial ramifications of infertility.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Infertility greatly impacts the lives of patients and couples who are trying to conceive. All too often, healthcare professionals underestimate patients' emotional distress when confronted with a fault in the process that they feel should be occurring easily and "naturally." In order to better assist individuals or couples who are affected by infertility, it is necessary for clinicians to have a good understanding of how infertility is caused in men and women, the treatments that can initially be prescribed for this condition in both sexes, and when to refer patients to infertility specialists or those specializing in assisted reproductive technology (ART).

The purpose of this course is to provide healthcare professionals with information regarding the etiology, risk factors, and physiology of infertility; making a diagnosis of infertility, including patient history and sexual habits, physical examination, and laboratory tests; treatments to improve fertility, including lifestyle change, medication interventions, and surgical options for men and women; and interventions beyond the scope of aiding natural reproduction, such as artificial insemination and in-vitro fertilization (IVF).

It is important to remember that there are often basic lifestyle factors that can be identified and some simple changes men and women can undertake that will increase their likelihood of conceiving. Realizing that there are relatively simple, nonmedical approaches to treating infertility, even without undergoing extensive testing, can reduce patients' stress and anxiety considerably and is an additional benefit along with reducing healthcare expenditures and decreasing the burden on the healthcare system.

DEFINING INFERTILITY

Men and women of reproductive age can be categorized as fertile, subfertile, or infertile in regards to their physiologic capability to conceive. It is most common for healthy couples younger than 35 years of age to conceive within six female reproductive cycles, after cessation of all birth control methods and initiation of regular unprotected sex; nearly 80% of couples fall into this category and are considered fertile [1]. Subfertile couples, who comprise about 10% of the population, will typically conceive between the 6th and 12th reproductive cycle [1]. The remaining 10% or so will be unable to conceive following 12 months of regular, unprotected sex and are considered infertile; this percentage varies based on age and several other factors that will be discussed later in this course [2].

The working definitions of infertility are rather nonscientific, including an inability of a man or woman to contribute to the conception of a child and "not being able to get pregnant despite having frequent, unprotected sex for at least one year [with the same male partner]" [3; 4]. This definition applies for most people, but in certain circumstances, six months of frequent unprotected sex without conception may be defined as infertility. When defining infertility in women, the term is sometimes also loosely applied to those unable to carry a pregnancy to full term; however, the term "impaired fecundity" (i.e., infertility and failure to carry to term combined) is more accurate.

There are two subcategories of infertility. Primary infertility describes individuals or couples who have never been able to conceive, and secondary infertility describes those who have successfully conceived and/or carried to full term prior to the current diagnosis of infertility [2]. Infertility in couples can be either a solely male or solely female fertility issue, or in some cases, both partners may be subfertile or infertile.

It is important to remember that not all women who want to become pregnant are in relationships or are heterosexual. For women without a male partner and who are undergoing insemination or other assisted reproduction procedures, the same definitions and categorizations apply; however, because many of these patients typically are nearing the end of their reproductive functionality, infertility in this group of patients, especially single heterosexual women, is a common condition.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Centers for Disease Control and Prevention and the U.S. Office of Population Affairs assert that primary care providers should offer help for patients who wish to achieve pregnancy and basic infertility services to improve the health of women, men, and infants.

(https://www.cdc.gov/mmwr/pdf/rr/rr6304.pdf. Last accessed June 16, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

EPIDEMIOLOGY

The percentage of couples with infertility in the United States is typical for modern Westernized countries, at between 10% and 15%, and from 1982 to 2002, was trending upwards in both men and women [3; 4]. Increased infertility rates were theoretically due to unhealthy lifestyles and possibly to excessive toxic environmental exposures, although an obvious reason in women was an increase in both age at first marriage and age at first birth in this two-decade period [4; 5]. It is worth noting that the incidence of infertility varies geographically; for example, men living in the greater Seattle area did not experience any decline in sperm count and quality over the same 20-year period that significant national declines were observed [6].

According to the 2006–2010 National Survey of Family Growth, national infertility rates among women have fluctuated since 2002, while infertility rates for men have essentially remained static [4; 7]. Impaired fecundity among married women 15 to 49 years of age increased from 11% in 1982 to 15% in 2002, and 16.3% in 2015–2019 [7]. Approximately 13.8% of all women in the same age group (compared with only married women) have impaired fecundity [7]. Infertility rates among married women declined from 8.5% in 1982 to 6.0% in 2006–2010 but then increased to 8.5% in 2015–2019 [4; 7]. Although it is generally unclear why variations in fertility and fecundity exist in actuality and as reflected in surveys, several ideas, including those already mentioned, have been proposed. For one, survey definitions and methodology can skew data, and alternately, advances in fertility treatments have been made [4]. These include both medical treatments and a greater awareness of the impact of lifestyle factors on fertility status.

As noted, infertility may be attributed to the male or female partner or to the couple. It is estimated that roughly one-third of couples' infertility is male-related, one-third is female-related, and the remaining one-third of cases are due to both partners being infertile [3].

FEMALE INFERTILITY

Age

Infertility is inexorably tied to age, and although increasing age causes reproductive decline in both men and women, it is especially important in the latter, as women have a definitive reproductive window that tapers to a distinct inability to conceive. Men, on the other hand, may be able to sire children well into their senior years. According to data from the Centers for Disease Control and Prevention (CDC) 2015–2019 National Survey of Family Growth (NSFG), 19.4% of married women 15 to 49 years of age in the United States have primary infertility; the percentage increases with age, with 12.6% of women 15 to 29 years of age, 22.1% of those 30 to 39 years of age, and 26.8% of those 40 to 49 years of age reporting primary infertility [7]. Secondary infertility is far less common among married women of all age groups, at around 6.0% [7].

Relationship Status

The majority of statistical information on infertility is regarding married women, but those who are married do not comprise a typical cross section of all women. Data on impaired fecundity from the 2015–2019 NSFG shows that 13.8% of women 15 to 49 years of age (of all marital statuses) and 16.3% of currently married women 15 to 49 years of age have impaired fecundity [7]. The percentage increases with increasing age, with impaired fecundity in 9.2% of women 15 to 29 years of age; 22.2% in women 30 to 39 years of age; and 33.4% in women 40 to 49 years of age [7]. Data from the most recent NSFG does not include a separate category for single women, but data from the 2010 version of the NSFG indicated that single women (7.9% impaired) were more fertile than their cohabiting (12.8% impaired) and married (12.1% impaired) counterparts [4]. In single women, the lower incidence of impaired fecundity may be because these women are using assisted reproduction, which bypasses some of the physiologic obstacles (e.g., fallopian tube obstruction, sperm problems) facing couples engaging in intercourse and who may be also dealing with psychological issues, which can exacerbate infertility. Single women undergoing insemination or assisted reproductive procedures also have likely undergone medical examinations prior to attempts at conception, which would uncover and address infertility risk factors.

There is a scarcity of infertility data on lesbian women, partially because it has been found that lesbian women tend to respond as "single" on surveys [8]. However, one study that specifically encouraged participants to accurately identify themselves according to their sexual identity found that lesbians tended to have an even lower incidence of impaired fecundity than heterosexual single women; it was theorized that this was mainly due to the fact that the lesbian women were statistically younger when insemination or other ART treatments occurred [8].

Race

Among married women in the United States 15 to 44 years of age, there is a slight variation in fertility status when race is taken into account. The overall infertility rate is 7.2% for Black women, 6.1% for Hispanic/Latina women, 5.6% for Asian women, and 5.5% for White women [4].

Education Level

Fertility also varies according to education level. Among married women with less than a high school education, the infertility rate is 5.7%; for those with a high school or partial college education, the rate is 6.4% and 4.5%, respectively; and for women with a Bachelor's degree, the rate is 7.9% [4]. The infertility rate for women with a Master's degree or higher is 6.0%.

Socioeconomic Status

Approximately 4.8% of married women who are living in households at or below the poverty level are infertile, while 5.3% of those in low-to-moderate income households are infertile. However, married women whose households earn four times the income of those living in poverty have the highest infertility rate (8.7%) [4].

MALE INFERTILITY

There is far less data available on male infertility, but it is estimated that the prevalence of infertility is similar among men and women with comparable socioeconomic/racial/age factors [3; 9]. It is also generally true that men older than 40 years of age are less fertile than their younger counterparts [3].

ASSISTED REPRODUCTIVE TECHNOLOGY

The use of ART has been increasing steadily since its inception, and today approximately 2% of infants are born using ART [10]. In 1998, there were 20,126 live birth deliveries (resulting in 28,851 live-born infants) using ART; in 2020, there were 75,023 (resulting in 79,942 live-born infants) [10]. Trends indicate that the use of ART will continue to grow for some time, especially because the incidence of infertility is still high in developed nations, including the United States, and because first marriage and first birth is delayed.

SIGNS AND SYMPTOMS

Of course, the primary physical symptom of infertility is an inability to become pregnant or to contribute to conception after 12 months of regular, unprotected sex; however, there are other signals that could indicate infertility. Having irregular menstrual periods, extremely light or heavy periods, or an absence of periods (amenorrhea) may be an indicator that there is a problem with ovulation. Severe menstrual cramps can also indicate a problem that may be causing infertility.

Men who have problems maintaining an erection or ejaculating normally are likely to have infertility problems. Retrograde ejaculation (i.e., little or no ejaculate with climax and cloudy urine after sex) is uncommon but could be a cause for infertility in some men.

Other signs and symptoms of infertility in men and women are related to specific disease, physiologic, and/or psychological conditions and will be discussed later in this course.

A REVIEW OF THE PHYSIOLOGY OF FERTILITY AND INFERTILITY

HORMONE SIGNALING AND PRODUCTION

Endocrine System

The hypothalamic-pituitary-adrenal (HPA) and the hypothalamic-pituitary-gonadal (HPG) axes, two of several endocrine processes, effectively form what is known colloquially as the reproductive axis, complete with hormone signaling, cross-regulation, and feedback loops. Normal human sexual development and reproductive capability relies heavily on a properly functioning reproductive axis from early in fetal life through puberty and into adulthood.

In order for the body to create the sex hormones most often associated with reproduction (estrogen, progesterone, and testosterone), several processes of the HPG/HPA axes are necessary. In regard to the HPG axis, neurons in the hypothalamus send out gonadotropin-releasing hormone (GnRH) that stimulates the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the adenohypophysis (the anterior portion of the pituitary gland), which in turn act on the gonads and the adrenal cortex. In regard to the HPA axis, adrenocorticotropin-releasing hormone (CRH) is also produced in the hypothalamus and stimulates the pituitary production of adrenocortical tropic hormone (ACTH), which acts on the adrenal gland. The adrenals and the gonads have thus been signaled to produce various amounts of corticosteroids (e.g., cortisol) and sex hormones (e.g., estrogen, progesterone, and testosterone), respectively, and to commence various processes (e.g., spermatogenesis, follicular maturation) dependent on certain factors, such as the physical/mental condition of the individual.

In addition to directly aiding reproductive processes, these hormones provide feedback to the previous structures of the axes, regulating their function. One example of hormone feedback is the FSH/estrogen loop, whereby FSH from the pituitary stimulates the maturation of follicles in the ovaries; the maturing follicles produce estrogen, which signals the pituitary to lower FSH production and increase LH [11]. This example illustrates the dual role of the ovary as an endocrine organ and a reproductive organ whose functions are closely linked.

As discussed, normal sexual development and reproductive function is heavily dependent on a properly functioning reproductive axis; pathology of the hypothalamus, pituitary, adrenals, or gonads can quickly lead to a hormone imbalance, malformation of the genitals, and/or infertility. Likewise, steroid hormone dysfunction in the regulatory feedback loops has great potential detriment to fertility; for example, male obesity can disrupt the HPG axis due to the high levels of aromatase in fat [12]. Aromatase in Sertoli cells normally converts testosterone to estradiol to regulate spermatogenesis. Increased aromatase activity converts too much testosterone into estrogen, and with reduced testosterone feedback to the adrenals, gonadotropin release is inhibited and sperm production suffers. (Female obesity is also associated with disruptions of the reproductive axis and infertility, as will be discussed later in this course [13].)

Thyroid Function

The thyroid gland and the hypothalamic-pituitary-thyroid (HPT) axis play another major part in human reproduction, and the HPT axis is interconnected with the HPA and HPG axes. Iodine from foods is combined with the amino acid tyrosine and converted by the thyroid to the hormones triiodothyronine (T3) and thyroxine (T4), which are necessary for cellular metabolism throughout the body. Thyroid hormones act directly on the testes and ovaries and indirectly by influencing GnRH, prolactin, and sex hormone-binding globulin (SHBG) production. Hypothyroidism and hyperthyroidism both can have a profound effect on ovarian function, menstrual cycling, and spermatogenesis, as can autoimmune thyroid diseases, such as Graves disease or Hashimoto disease, which can cause thyroid hormone deficiencies. Thyroid diseases affect millions of Americans but are far more common in women than in men [14]. Iodine deficiency, one cause of thyroid disorders, is associated with female infertility and impaired fecundity.

According to the American Society for Reproductive Medicine, currently available data support that it is reasonable to test thyroid-stimulating hormone in infertile women attempting pregnancy.

(https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/subclinical_hypothyroidism_in_the_infertile_female_population.pdf. Last accessed June 16, 2023.)

Level of Evidence: B (There is fair evidence to support the recommendation.)

Sex Hormone-Binding Globulin

SHBG is also a major factor in fertility, as testosterone and estrogen (estradiol) bind to SHBG and are transported through the bloodstream. The correct amount of SHBG, which is produced in large part by the liver, is necessary to maintain proper hormonal balance. Conditions that affect the liver, such as diabetes and obesity, can have a negative effect on SHBG levels, leading to excessive estrogen in men and increased androgens in women [15].

Endocannabinoid System

A growing body of evidence shows that the endocannabinoid system plays a significant role in human development and reproduction, including hormone regulation; oocyte production; sperm production, motility, and capacitation; sperm-oviduct interactions; acrosome reactions; embryo oviductal transport; blastocyst implantation; post-implantation embryonic growth; and placental development [16; 17; 18; 19; 20]. The endocannabinoid system is made up of endogenous ligands, ligand-metabolizing enzymes, and cannabinoid receptors, of which the receptor CB1 is the most abundant G protein-coupled receptor in the brain; the CB2 receptor is mostly found in the immune system [21]. It is now known that processes previously thought to be signaled and regulated only by steroid hormones and the reproductive axis are, at least in part, regulated by endogenous cannabinoid neurotransmitters and the endocannabinoid system.

The first endocannabinoid to be discovered was anandamide in 1992, with 2-arachidonoylglycerol discovered soon after; these neurotransmitters are biosynthesized from arachidonic acid, a polyunsaturated omega-6 fatty acid [21]. It is suggested that a deficiency of arachidonic acid, ingestion of obesity drugs (e.g., rimonabant) that compete for cannabinoid-receptor binding, or use of other exogenous cannabinoids (e.g., cannabis, dronabinol) can interfere with the endocannabinoid system and cause infertility. The endocannabinoid system is thought to also modulate the HPA axis and reduce the negative effects of stress hormones, among other functions, including pain and inflammation reduction, autonomic function and immunity, neuroprotection, tumor apoptosis, and feeding and hunger [21]. Further research is necessary to better understand the endocannabinoid system's effect on human reproduction and to learn how to utilize the system to positively affect fertility status. More information on the endocannabinoid system will be given in relation to cannabis use and its effect on fertility later in this course.

FEMALE REPRODUCTION

The reproductive span for women is naturally confined to a set period between menarche and menopause and is considered to be between 15 and 45 years of age; however, women's peak fertility occurs in their early- to mid-20s. Female reproductive potential and age of menopause (51 years of age, on average) is dependent on ovarian follicle reserve (i.e., quality and quantity of primordial follicles); as a result of natural and induced variations in ovarian reserve among women, reproductive span, age of peak fertility, and age at menopause varies greatly as well [22].

Folliculogenesis

At birth, there are approximately 2 million primordial follicles or primary oocytes in the ovaries, but by menarche that number has already declined to around 300,000 to 500,000 due to a natural exponential depletion process called atresia [22; 23; 24]. At 25 years of age there are probably around 60,000, and by 40 years of age there are only 6,000 or so remaining. From birth, primordial follicles enter the growing follicle pool, but unless they are stimulated by FSH, which begins to occur around puberty, the follicles degenerate in the ovaries. A common misconception is that there are a set number of follicles that coincide with the exact number of menstrual cycles a woman will have during the course of her reproductive years. In reality, younger women have hundreds of follicles in the growing pool each year, which can be stimulated simultaneously, but usually only a small cohort (about five to seven) will be recruited by FSH, and a single dominant follicle will become a mature oocyte (female gamete) during gametogenesis. Therefore, the biologic design allows

a great many primary oocytes to be lost each year in the selection process, while only about 400 will ever become fully mature. Menopause results from an exhaustion of the primordial follicle pool or an inability for recruitment, and therefore a lack of hormone-producing, growing follicles in the ovaries.

Fallopian Tube Function

Besides ovarian function, fallopian tube patency and function are particularly important to natural reproduction. There are two types of cells found in the epithelium of the fallopian tube: ciliated cells and peg cells. Ciliated cells are the most numerous, especially near the infundibulum at the distal end of the tube and the ampulla at the midsegment, and are responsible for egg transport to the uterus; the expression of cilia is increased by estrogen. The second type of cells, peg cells, produces fluid that aids the transport of sperm toward the oocyte at the fimbriated end and provides nutrients for the sperm, oocyte, and zygote. Peg cell secretions also aid in sperm capacitation. The negative side of this function is that infections can also be carried deep into the fallopian tube. Estrogen enhances the fluid secretion, and progesterone increases the number of peg cells.

The Menstrual Cycle

Controlled by the endocrine system, proper menstrual cycling requires a careful balance of hormones, primarily FSH, LH, progesterone, and estrogen [25]. The menstrual cycle involves concurrent processes of the uterus (endometrial shedding and growth), fallopian tubes (growth of cilia and peg cell fluid secretion), and ovaries (follicular maturation), which are signaled and regulated by varying levels of these sex hormones. The first phase of the ovulatory cycle, known as the follicular phase, corresponds with the onset of menses and the menstrual proliferative phase (growing uterine lining) and lasts for approximately 14 days. The second phase, ovulation, typically occurs on day 14. Finally, the luteal phase corresponds with the secretory phase, from days 14 to 28.

FSH stimulation of a cohort of follicles begins early in the follicular phase. The follicles begin to release estrogen, which steadily rises until just before ovulation, when estradiol peaks. Estrogen causes the endometrium to grow and become enriched with blood and glands. As discussed earlier, the estrogen feedback causes lowered FSH and increased LH. Just before the second stage (ovulation), the LH surge causes weakening of the follicle wall in the ovary, readying it for release, and then ovulation at LH peak. During the luteal phase, the corpus luteum produces a significant amount of progesterone, enabling the endometrium to become more receptive to the blastocyst in the event of fertilization, increasing basal body temperature, and preventing uterine contractions and the development of new follicles [26]. If fertilization of the oocyte does not take place, the rise in progesterone signals the inhibition of GnRH, which limits the production of additional progesterone. Following this, the corpus luteum degenerates, the uterine lining begins to die, and uterine cramps ensue.

MALE REPRODUCTION

Reproductive potency for males usually begins around 12 to 14 years of age and, strictly speaking, is not limited by age, but also peaks in the early- to mid-20s. A healthy male at his sexual peak will produce 12 billion sperm per month. Each ejaculate contains roughly 300 million sperm, but even under the best circumstances only about 200 will gain proximity to the ovum [27].

Spermatogenesis

The male counterpart of an oocyte (female gamete) is spermatozoa (male gamete) and is produced through an analogous process of gametogenesis, or more specifically, spermatogenesis. Unlike oogenesis, whereby oocytes are matured from a depleting store of primordial follicles created before birth, sperm are continually generated after the onset of puberty in healthy males under the influence of sex hormones. Spermatogenesis begins with germ cells containing 46 chromosomes, and through processes of meiosis and mitosis, taking place initially in the testes

and finally in the epididymis, mature sperm with 23 chromosomes are created and stored until they are ejaculated. Spermatogenesis, from germ cell to spermatozoa, takes a total of 64 days [28].

During the ejaculatory process, sperm is mixed first with seminal fluid (to gain an energy source and alkalinity, which aid survival in the acidic vaginal environment) and then with prostatic fluid (to aid sperm propulsion) to finally become semen [27]. Problems with spermatogenesis and/or seminal or prostatic fluid composition can lead to male infertility.

Two important cell types in the testes are Sertoli cells, located on the inner walls of the seminiferous tubes, and Leydig cells, found adjacent to the seminiferous tubes. Leydig cells release androgens (most notably testosterone) under the influence of LH; prolactin modulates the expression of Leydig cell LH receptors. Sertoli cells, or "nurse cells," are responsible for the nourishment and growth of immature germ cells (spermatogonium) into spermatids and for the transport of spermatids to the epididymis for the final stage of spermatogenesis, where they will become motile and mature. Sertoli cells are stimulated by FSH and also have a secretory role. Inhibin and activins (to regulate FSH), testosterone-binding globulin (to accumulate testosterone for sperm development), estradiol (to regulate spermatogenesis), and anti-Müllerian hormone (to prevent Müllerian duct development), among others, are secreted by Sertoli cells.

SEXUAL REPRODUCTION

Natural conception involves one relatively healthy male haploid gamete (i.e., sperm) fertilizing a similarly viable female haploid gamete (i.e., mature oocyte) in the distal portion of the fallopian tube, thereby creating a diploid zygote with 46 chromosomes that begins to undergo mitosis, or cleavage, to become a blastocyst that implants in the endometrium. Healthy gametes are not the only factors influencing the ability to become pregnant. The fallopian tubes must be healthy and patent, allowing the unimpeded passage of either sperm or the zygote. The uterus must also be properly shaped, to a certain degree, and the endometrium should be neither too thin or too thick and free from adhesions, polyps, and submucous fibroids [29]. Abnormal cervical mucus is rarely the cause of infertility, except in the case of cervical stenosis or chronic cervicitis [30].

In healthy couples, when both partners are younger than 35 years of age and having sex regularly, the chance of the woman becoming pregnant (i.e., fertilization and blastocyst implantation) is 22% to 25% per month; beyond 35 years of age—and especially after women reach 40 years of age—the likelihood of pregnancy drops to between 2% and 8% per monthly cycle [31]. However, it is important to remember that these figures are averages and female patients could have many fertile years ahead of them but are being affected by any number of factors that are decreasing their chances of conception. Based on infertility statistics, a majority of individuals have adequate reproductive function, and given the right circumstances, natural conception is expected to occur within one to six menstrual cycles [1].

ETIOLOGIES OF INFERTILITY

There are many potential causes of infertility; however, the three most prevalent categories are ovulatory disorders, fallopian tube patency problems, and problems with sperm and/or semen [32]. Oxidative stress, imparted mainly by an unhealthy lifestyle but also due to certain environmental factors, is an increasingly common pathology affecting fertility in both men and women and is responsible for damage to oocytes, sperm, and reproductive tissues. It should be noted that because the majority of the reproductive burden and relative complexity of processes concern women's reproductive capacity, there is substantially more research and information regarding female infertility.

CAUSES OF OVULATORY AMENORRHEA	
Diagnoses	**Causes**
Congenital genital abnormalities	Cervical stenosis (rare) Imperforate hymen Pseudohermaphroditism Transverse vaginal septum Vaginal or uterine aplasia (e.g., Müllerian agenesis)
Acquired uterine abnormalities	Asherman syndrome Endometrial tuberculosis Obstructive fibroids and polyps
Source: [35]	*Table 1*

OVULATORY DISORDERS

Ovulatory Amenorrhea

Amenorrhea, or absence of menstrual periods, can either be ovulatory or anovulatory. Although both types cause female infertility, anovulation is the most common cause of infertility overall [33].

Although rare, ovulation without menses is usually caused by obstructive disorders that can either be congenital, a result of arrested development of the Müllerian ducts, or acquired later in life, such as from surgery or infection (***Table 1***). Approximately 1 in 4,000 women are born with congenital vaginal agenesis (no vagina) and other variations of deformity to the vagina and uterus (e.g., Müllerian agenesis), though many of these women have fully functioning ovaries and secondary sexual features [34].

Anovulatory Amenorrhea

Anovulation, or a complete lack of ovulation, is typically caused by disorders of the HPA or hypothalamic-pituitary-ovarian axes. Extreme stress, exercise-induced stress, anorexia, obesity, malnutrition, diabetes, drug or alcohol use, and polycystic ovary syndrome (PCOS) are general risk factors for anovulatory amenorrhea and will be discussed later in this course. ***Table 2*** lists several examples of conditions or causal factors that commonly lead to anovulation and amenorrhea according to which endocrine structure is affected.

Primary Ovarian Insufficiency

About 1 in 100 women experience primary ovarian insufficiency between 30 and 39 years of age [23]. Women 15 to 29 years of age experience the condition at rates of about 1 in 1,000. The terms "early/premature menopause" are sometimes used colloquially; however, these are misnomers. Normal biologic menopause occurs at around 51 years of age, on average, and is caused by hormonal changes relating to the natural exponential depletion of follicles that typically follows 35 years of menstrual cycling. Primary ovarian insufficiency is instead an ovarian follicular disorder with two basic variations: premature follicular depletion and follicular dysfunction. Primary ovarian insufficiency is sometimes referred to as premature ovarian aging or failure.

Follicular depletion describes an unusually hasty loss of the finite number of follicles contained in the ovaries and can be caused by exposure to environmental toxins (e.g., heavy metals, industrial chemicals, pesticides, welding fumes), cancer treatments (e.g., chemotherapy, radiation therapy), certain viruses, or chromosomal defects/genetic factors (e.g., Turner syndrome, fragile X syndrome). There is also a 10% chance of developing primary ovarian insufficiency if a family member has the condition [11; 36].

CAUSES OF ANOVULATORY AMENORRHEA	
Diagnoses	**Causes**
Hypothalamic dysfunction, structural	Genetic disorders (e.g., congenital gonadotropin-releasing hormone deficiency, Prader-Willi syndrome) Infiltrative disorders of the hypothalamus (e.g., Langerhans cell granulomatosis, lymphoma, sarcoidosis, tuberculosis) Irradiation of the hypothalamus Traumatic brain injury Tumors of the hypothalamus
Hypothalamic dysfunction, functional	Cachexia Chronic disorders, particularly respiratory, gastrointestinal, hematologic, renal, or hepatic (e.g., Crohn disease, cystic fibrosis, sickle cell disease, thalassemia major) Dieting Drug abuse (e.g., alcohol, cocaine, cannabis, opioids) Eating disorders (e.g., anorexia nervosa, bulimia) Excessive exercise HIV infection Immunodeficiency Psychiatric disorders (e.g., stress, depression, obsessive-compulsive disorder, schizophrenia) Psychoactive drugs Undernutrition
Pituitary dysfunction	Aneurysms of the pituitary Hyperprolactinemia[a] Idiopathic hypogonadotropic hypogonadism Infiltrative disorders of the pituitary (e.g., hemochromatosis, Langerhans cell granulomatosis, sarcoidosis, tuberculosis) Isolated gonadotropin deficiency Kallmann syndrome (hypogonadotropic hypogonadism with anosmia) Postpartum pituitary necrosis (Sheehan syndrome) Traumatic brain injury Tumors of the brain (e.g., meningioma, craniopharyngioma, gliomas) Tumors of the pituitary (e.g., microadenoma)
Ovarian dysfunction	Autoimmune disorders (e.g., autoimmune oophoritis resulting from myasthenia gravis, thyroiditis, or vitiligo) Chemotherapy Genetic abnormalities, including chromosomal abnormalities (e.g., congenital thymic aplasia, fragile X syndrome, Turner syndrome) Gonadal dysgenesis (incomplete ovarian development, sometimes secondary to genetic disorders) Irradiation to pelvis Metabolic disorders (e.g., Addison disease, diabetes, galactosemia) Viral infections (e.g., mumps)
Other endocrine dysfunction	Androgen insensitivity syndrome (testicular feminization) Congenital adrenal virilism (congenital adrenal hyperplasia [e.g., due to 17-hydroxylase deficiency or 17,20-lyase deficiency] or adult-onset adrenal virilism)[b] Cushing syndrome[b,c] Drug-induced virilization (e.g., by androgens, antidepressants, or high-dose progestins)[b] Hyperthyroidism Hypothyroidism Obesity (causes excess extraglandular production of estrogen) Polycystic ovary syndrome[b] True hermaphroditism[b] Tumors producing androgens (usually ovarian or adrenal)[b] Tumors producing estrogens or tumors producing human chorionic gonadotropin (gestational trophoblastic disease)

[a]Hyperprolactinemia due to other conditions (e.g., hypothyroidism, use of certain drugs) may also cause amenorrhea.
[b]Females with these disorders may have virilization or ambiguous genitals.
[c]Virilization may occur in Cushing syndrome secondary to an adrenal tumor.

Source: [35] *Table 2*

Follicular dysfunction describes conditions in which follicles in the ovaries are failing to reach maturity. Primary ovarian insufficiency most often occurs due to autoimmune diseases, such as antiphospholipid syndrome, but occasionally can also be due to inadequate gonadotropin signaling, eating disorders, or thyroid dysfunction [2; 11; 23]. Most women with primary ovarian insufficiency have sufficient levels of FSH; therefore, the ovaries do not respond to FSH supplementation.

The HPG axis (specifically, the FSH/estrogen feedback loop) becomes seriously disrupted in women with primary ovarian insufficiency because the follicles, which would normally produce estrogen, are non-functioning. Individuals with primary ovarian insufficiency will have a lack of estrogen and an excess of FSH that can be confirmed in laboratory tests. Most women with primary ovarian insufficiency are infertile, and their ovaries do not respond to fertility treatments [11]. Hormone replacement strategies have helped a small number of women with primary ovarian insufficiency to become pregnant [23].

Polycystic Ovary Syndrome

PCOS is a common cause of female infertility, and it is estimated that between 1 in 10 and 1 in 20 women of childbearing age (or approximately 5 million American women) are affected by varying degrees of PCOS [37]. The name is derived from the characteristic appearance of the ovaries in most women with this condition; many roughly pea-sized cysts develop and remain embedded on the ovary, usually along the outer edge. In a normal ovulatory cycle, an egg develops within a follicle and the follicle ruptures and releases the egg during ovulation. When a fully mature egg fails to develop due to PCOS, the follicle remains unruptured in the ovaries, which become more enlarged with each successive cycle.

Although the exact cause of PCOS is not yet fully understood, there are several factors that are thought to contribute to its development, including [38; 39]:

- Hyperinsulinemia: When there are high levels of circulating insulin, due to insulin resistance (as in patients with prediabetes or poorly controlled or undiagnosed diabetes), a hormone imbalance occurs and the ovaries produce elevated levels of androgens. These androgens are responsible for the failure of ovum maturity. Lower levels of estrogen and LH, coupled with elevated FSH, further disrupt normal ovulation and the reproductive axis.
- Low-grade inflammation: Insulin resistance can be caused by an inflammatory response that can be triggered by certain foods in predisposed individuals. The high circulating insulin levels in those with chronic inflammation can lead to PCOS.
- Heredity: PCOS is possibly genetic, and having a relative with PCOS is a risk factor for the disorder.
- Abnormal fetal development: Exposure to excessive levels of androgen in the womb may contribute to PCOS by creating a male pattern of fat distribution in women, leading to insulin resistance and low-grade inflammation.

Symptoms of PCOS include hirsutism, hyperandrogenism, male-pattern baldness, adult acne or severe adolescent acne, irregular periods, anovulation, infertility, and lipid abnormalities, but there are few or no obvious symptoms in some patients [38; 39; 40]. Obese individuals are more likely to have PCOS; however, one study found that the likelihood of obese adolescents developing hyperandrogenemia and PCOS was not exclusively linked to body mass index (BMI) but instead more closely followed hyperinsulinemia and hormone imbalance trends [41]. Most research supports the theory that body type/shape and fat distribution (i.e., waist-to-hip ratio) are more relevant to reproductive health than mere BMI score, although having a high BMI is generally considered a risk factor for PCOS [39].

Patients' symptoms vary greatly upon presentation, and because the symptoms are similar to many other conditions, diagnosis can be difficult. Information that can aid a diagnosis includes [39]:

- Interview: Unusual weight gain, menstrual cycle, family history
- Physical assessment: Acne, hirsutism, BMI, distribution of body fat (i.e., waist-to-hip ratio), pelvic exam (to gauge ovary size)
- Laboratory tests: LH, FSH, estrogens, androgens, glucose, and insulin levels
- Ultrasound examination

TUBAL OCCLUSION

Fallopian tube obstruction is a pathology found in roughly 20% to 30% of women with infertility [36; 42]. The pathophysiology of tubal infertility includes adhesions, inflammation, cysts, polyps, hydrosalpinx, and/or scarring of the oviducts or fimbriae resulting from pelvic inflammatory disease (PID), a generalized constellation of upper reproductive tract disease; salpingitis; peritoneal infection, such as appendicitis with rupture or general peritonitis; and endometriosis. Rarely, congenital defects, such as maldescent or absence of fallopian tubes, are the cause of patency issues.

Proximal occlusion refers to tubal damage near the uterus and is the most easily treated. Distal occlusion refers to tubal obstruction near the ovaries and is unfortunately more common than proximal occlusion. Peritubal occlusion refers to obstruction caused by peritoneal inflammation or adhesions on the exterior fallopian tubes. Midsegment occlusion also can occur from infection but is typically caused by sterilization procedures.

Salpingitis and Hydrosalpinx

Salpingitis is infection and inflammation of the fallopian tubes, fimbriae, and/or ovaries due to various bacterial infections (e.g., streptococcus, staphylococcus, gonococcus, *Escherichia coli*, tuberculosis, actinomycosis, schistosomiasis, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*) ascended from the vagina, cervix, or uterus, such as those possibly caused by sexually transmitted infections (STIs), surgical abortion, childbirth, intrauterine device (IUD) insertion or removal, upper genital diagnostic procedures, surgery, and other procedures [43]. Ascent of the infection may be attributed to several factors, including sexual intercourse (e.g., bacteria "rides" sexual fluids into the uterus—especially during female orgasm with rhythmic uterine contraction, or sex during ovulation, when the cervical os is enlarged), other "silent" rhythmic uterine contractions, menstruation or retrograde menses, vaginal douching, young age (i.e., immature cervix), and the use of antibiotics, which can cause a disruption of normal vaginal flora. Salpingitis also causes lesions and scarring that may interfere with normal fallopian functioning and is a typical precursor to PID.

Tubal infection usually leads to an increase in peg cell secretions. These secretions normally reabsorb; however, the accumulation of excessive fluid can cause a hydrosalpinx—a collection of fluid that seals the fimbrial end of the tube. Despite the proximal end of the fallopian tube remaining open after an infection resolves, the hydrosalpinx does not drain and can eventually cause tubal distension and distortion of the reproductive tract [43]. A hydrosalpinx can form without noticeable infection or symptoms and may only be discovered upon investigation of infertility. Hysterosalpingography may be used to detect the condition because the proximal portion of the tube remains patent. Because hysterosalpingography involves filling the fallopian tubes with dye or medium, it may also be useful in improving the chances of conception, possibly by "flushing" the tubes of potential or partial blockages. A meta-analysis of 13 trials found a slightly increased chance

of pregnancy and live birth after the procedure when an oil-based medium was used compared with no intervention at all [44].

Pelvic Inflammatory Disease

PID is an inflammatory reaction of the upper reproductive tract or pelvic/peritoneal area to one of a variety of invasive organisms but is typically caused by bacterial infection with, in order of prevalence, *C. trachomatis*, *N. gonorrhoeae*, multibacterial infection, and mycoplasmas. It usually affects the distal portion of the fallopian tube [42]. The pathophysiology of PID usually involves salpingitis. Salpingitis and the resulting inflammation can cause scar tissue to build up on the previously healthy epithelial lining of the fallopian tube, creating a partial or total occlusion and inhibiting the fertilization of an oocyte by sperm cells. However, any invasive procedure of the upper genitalia (e.g., dilation and curettage, biopsy) has the potential to cause PID. Other infections or disorders of the pelvic or abdominal area also have the potential to cause PID. The anaerobe *Bacteroides fragilis* is especially destructive to the fallopian tubes, and many women with PID are found to have bacterial vaginosis [45].

Scarring or lesions can also inhibit the normal function of the fallopian tubes' cilia and, therefore, the passage of the zygote, greatly increasing the risk of ectopic pregnancy in the event of fertilization. PID is responsible for a large proportion of ectopic pregnancies occurring every year [36; 46; 47].

Up to one out of every five women with PID from any cause, including bacterial STIs, will become infertile [48]. It is estimated that there are nearly 1 million cases of PID every year in the United States [46]. These two statistics combined indicate that up to 200,000 women may become infertile each year due to PID and the associated tubal damage [36; 46; 48]. Infertility is found at higher rates with each successive episode of PID, with rates of 12%, 23%, and 54%, from the first, second, and third episodes, respectively, noted in a literature review of studies of women with a history of pelvic disease [47].

Risk factors for PID include multiple sex partners, having a sex partner that has more than one sex partner, young age, young age at first intercourse, the use of an IUD, vaginal douching, the presence of bacterial vaginosis, and a history of an STI [46; 49]. Adolescents are especially susceptible to the development of PID; one out of eight sexually active girls will have PID before 20 years of age [46; 50]. Unsafe sexual practices and biologic factors both contribute to the increased incidence in this population. For example, the female cervix is not fully mature in shape, size, and function until 25 years of age, leaving the upper genital tract of sexually active younger women more susceptible to bacterial infections, such as chlamydia and gonorrhea [46; 47].

It is critical to teach patients that vaginal douching is harmful, and even more so for those younger than 25 years of age, because it can force existing (even mild) bacterial vaginal infections into the upper reproductive tract, causing endometrial infection and acute salpingitis. One study found that women 18 to 24 years of age who douched had a 50% chance of reduced monthly fertility compared with women who did not douche. The risk of douching-related reduced monthly fertility was 29% in women 25 to 29 years of age and 6% among women 30 to 39 years of age [51].

Endometriosis

Endometriosis is a chronic disease that causes abnormal growth of endometrial tissue outside of the uterus, on the bladder, or on the bowels. It is estimated that endometriosis affects nearly 5% of women in the United States and causes infertility in up to 50% of those women [52; 53]. Approximately 25% to 50% of women with infertility are found to have endometriosis. Adhesions, inflammation, and distortion of the pelvic anatomy, in advanced cases of endometriosis, are responsible for mechanical infertility, but there are also thought to be endocrine factors at work in early cases (e.g., luteinized unruptured follicle syndrome, luteal phase defect, abnormal follicular growth, premature and multiple LH surges). A study published in 2010 found that monocyte chemotactic protein (MCP)-1 and perito-

neal leptin play important roles in the pathogenesis of early-stage endometriosis-related infertility [42]. However, the causes of endometriosis-related infertility in the early stages of the disorder are still poorly understood, as are the causes of endometriosis itself [53].

Medical Procedures and Other Illnesses

Tubal infertility as a result of bacterial infections that are caused, translocated, or reactivated by medical procedures involving the female upper reproductive tract, such as surgical abortions, IUD insertion and removal, natural and cesarean childbirth, laparoscopy, hysteroscopy, and tubal operations, is not uncommon. Medical procedures and infections of the pelvic area in general also increase infertility risk. One study found that adhesions form in approximately 75% of women undergoing pelvic surgery [36].

Appendicitis with rupture causes an almost fivefold increase in the chance of tubal infertility, but emergency removal of the appendix without rupture is not associated with greatly increased risk of infertility [36; 54]. Inflammatory bowel disease is also associated with infertility, as is tuberculosis infection of the fallopian tubes [36].

SPERM DISORDERS

In most instances, testicular volume, along with proper Leydig cell and seminiferous function, correlates directly with sperm density, total sperm count, and sperm motility [55]. Upon analysis of semen, the most common findings indicating male-factor infertility are azoospermia, oligospermia, teratospermia (poor sperm morphology or abnormally shaped sperm), asthenozoospermia (poor sperm motility), pyospermia/leukocytospermia (high levels of seminal fluid leukocytes), and sperm with high DNA fragmentation. The causes of these conditions are usually dysfunction of Leydig or Sertoli cells due to hormone deficiency or imbalance, congenital defects, mechanical testicular damage, or damage caused by heat, radiation, oxidation, infections, or reproductive toxins. In other cases, problems with blood flow to and from the testes may pose a threat to spermatogenesis, as with varicoceles. Abnormal seminal fluid fructose level and/or pH are also potential causes of infertility.

Varicocele

A varicocele is an abnormal dilation of any of the veins of the spermatic cord just above the testicle (usually on the left side), similar to a varicose vein. The condition is generally asymptomatic, but pain may occasionally exist. Varicocele leading to testicular atrophy is the most common cause of azoo- and oligospermia; the incidence of varicocele in men with primary and secondary infertility is approximately 25% and 75%, respectively [56]. Varicoceles in adolescents and young adults have been associated with significant loss of testicular volume and growth arrest of the testes, the risk of which increases with the size of the varicocele [57; 58]. These individuals should be monitored with physical examination and semen analyses to detect changes in testicular function, as earlier treatment will increase the likelihood of recovering normal spermatogenetic function [59; 60].

The causes of atrophy and lowered sperm count due to this condition are mainly theoretical—all have evidence for and against—and include increased pressure and temperature, disruption of the HPG axis, reflux of renal and adrenal metabolites down the spermatic vein, hypoxia, and oxidative damage [61]. High scrotal temperatures and oxidative damage are the leading theories. Smoking, a source of oxidative damage, greatly increases the risk of impaired spermatogenesis in men with this condition. Varicoceles are also associated with a decline in Leydig cell function and poor sperm quality [61]. Additionally, lowered testosterone levels are found in men older than 30 years of age with varicocele [62].

Leydig Cell Dysfunction

Another leading cause of infertility is dysfunction or failure of Leydig cells [63]. Although the role of Leydig cell dysfunction in male infertility has not been clearly elucidated, some studies have indicated that Leydig cell function is impaired in severely oligospermic men [64; 65]. Leydig cell dysfunction is characterized by lower levels of serum testosterone, circulating free testosterone, and testosterone/LH ratios and higher levels of serum LH, estradiol, and estradiol/testosterone ratios. In one study conducted in Denmark in 2004, researchers compared the levels of these hormones in fertile men to those in men with infertility of unknown origin [65]. The study indicated that the men with infertility showed significant signs of Leydig cell impairment, the extent of which correlated with decreased spermatogenesis. However, it is important to note that the relationship in this case may not be causal; there may be a common cause of both Leydig cell dysfunction and decreased spermatogenesis, possibly testicular dysgenesis in utero [65].

Sertoli Cell-Only Syndrome and Klinefelter Syndrome

Sertoli cell-only syndrome (SCOS) is a condition whereby Leydig cells are not present along the seminiferous tubes, causing a severe reduction of spermatogenesis. Patients are typically 20 to 40 years of age and normal on physical examination, with the condition presenting with infertility without sexual abnormality. Diagnosis usually is made based on findings of testicular biopsy. An estimated 5% to 10% of men with infertility may have SCOS [66]. On occasion, pockets of sperm are found; however, the individual is almost always azoospermic. There is no treatment for SCOS, and the cause of the condition is yet unknown.

A very high percentage of men with Klinefelter syndrome have SCOS. Klinefelter syndrome is the most common chromosomal defect in men, affecting approximately 250,000 men in the United States [26]. It is characterized by hypogonadism (i.e., small penis and testes, low testosterone, oligo- or azoospermia), feminine distribution of fat and pubic hair, gynecomastia, and lack of facial and body hair.

Tubal Disorders

Congenital disorders of the tubal structure connecting the testicles to the prostate can result in effective sterility [67]. One example is the congenital abnormality of the Wolffian (mesonephric) duct, whereby it fails to properly develop into the vas deferens and/or seminal vesicle due to fetal testosterone deficiency, preventing the addition of semen and passage of sperm. The testicles, spermatogenesis, and endocrine function are usually normal, but sperm morphology may be affected. Often the epididymis is swollen with sperm. Remedies are intracytoplasmic sperm injection (ICSI) or reconstruction of the tubes.

Seminal Fluid Disorders

Seminal fluid that has low fructose content cannot provide sperm with the necessary energy required to gain proximity to the oocyte [68]. Low seminal fructose levels are more common in older men than younger men and are primarily caused by androgen deficiency or inflammation of the seminal vesicles [69]. Treatment with chorionic gonadotropin is recommended.

OTHER CAUSES OF INFERTILITY

Oxidative Stress

When the body's protective antioxidant defenses become depleted or reactive oxygen species are in excess, cellular damage can occur due to oxidation. Oxidative stress upon sperm is a pathology seen in roughly 50% of men with infertility [70]. Similarly, oxidation can damage oocytes during folliculogenesis. Though reactive oxygen species are byproducts of normal metabolism, several factors can lead to high levels of reactive oxygen species in semen and in the reproductive organs, including [70; 71]:

- Alcohol, tobacco, and drug use
- Medication use (e.g., aspirin, acetaminophen)
- Underweight, extreme exercise, obesity, and poor diet
- Exposure to heavy metals, pesticides, herbicides, or petrochemicals
- Autoimmune disorders, chronic disease or illness, and infections

- Decreased levels of antioxidants or antioxidant cofactors (e.g., selenium, copper, zinc) due to any of the aforementioned factors
- Undescended or malformed testicles, testicular torsion, and varicocele

Oxygen ions, peroxides, and free radicals can damage gametes and cause infertility in one of two ways. DNA can be damaged, causing defective DNA to be passed along and increasing the risk of miscarriage. Alternatively, gametes can suffer mechanical injury [70]. For example, acrosome damage can impair the ability of sperm to fuse with the oocyte and damage to the tail can cause reduced sperm motility.

Heat

Prolonged exposure to high temperatures, as found in hot tubs, hot baths, or saunas, is a factor for decreased fertility in men [72]. This type of infertility may be reversible. Occupational exposure to prolonged elevated temperatures can have similar negative effects [73].

IMPAIRED FERTILITY IN CANCER SURVIVORS

Gonadal dysfunction can occur in both boys and girls as a result of alkylating agents or radiation therapy given to treat childhood cancers [74; 75; 76]. In boys, testicular dysfunction may include delayed or arrested puberty, oligospermia, azoospermia, or infertility. In girls, ovarian dysfunction may include delayed or arrested puberty, premature menopause, or infertility [74; 75; 76; 77; 78]. The risk is dose-dependent and is increased when an alkylating agent is used in combination with radiation or an anthracycline [76; 77]. The relative risk for male infertility has been reported to be 9 times higher in association with use of an alkylating agent and 10.6 times higher in association with both an alkylating agent and an anthracycline [79].

Cranial radiation is correlated with an increased risk for premature puberty, especially for girls treated before 8 years of age [74]. The risk of infertility is low and is directly related to gonadal exposure to radiation and age at the time of treatment [80; 81]. The possibility of maintaining gonadal function in the presence of higher cumulative doses of alkylating agents is greater for girls than for boys [76].

The annual history and physical for childhood cancer survivors at high risk for gonadal dysfunction should include evaluation of the puberty stage and pace, sexual function, and Tanner assessment [76]. Baseline levels of FSH, LH, and estradiol (girls) or testosterone (boys) should be determined at 13 years of age for girls or 14 years of age for boys and as clinically indicated [76].

RISK FACTORS

Although there are certain causes of infertility that are sex specific, a host of other risk factors affect men and women alike, including poor nutrition; eating disorders; obesity; intense exercise; stress; drug, alcohol, and tobacco use; exposure to certain medications, environmental toxins, or radiation; and chronic diseases, such as diabetes [2].

OBESITY

Obesity is an epidemic in the United States. Statistics from 2017–2020 show that 40.3% of men and 39.7% of women in the United States between 20 and 39 years of age are obese (i.e., BMI greater than 30), with greater prevalence among certain racial/ethnic minorities [82]. It is inevitable that with numbers this high, many individuals will have complications arising from their excessive weight.

Much attention has been focused on the evidence that obesity is a contributing factor in many disease conditions, including diabetes, cardiovascular disease, cancer, and arthritis, but what is less widely known is that obesity contributes significantly to infertility in both men and women [83; 84; 85; 86; 87]. Obesity in women can cause menstrual irregularities and pelvic organ prolapse and increases the risk of endometrial polyps, symptomatic fibroids, PCOS, and anovulation [83; 88; 89; 90; 91]. PCOS accounts for a majority of ovulation disorders, and a significant number of women with PCOS are

obese. Additionally, fetal morbidity and mortality are increased with obesity [90; 92]. ART treatments are also far less successful in patients with a BMI greater than 30 [88; 90].

A 2010 study of 56 obese women around 30 years of age (with an average BMI of 37.7) found that the 40 anovulatory women in the research group had larger waist circumferences and significantly more abdominal and trunk fat than the ovulatory women [89]. Conditions that affect fertility, such as PCOS, diabetes, and hypertension, are particularly common among women with a central distribution of body fat (i.e., "apple shaped") compared with those that are "pear shaped" [39]. Another study of obese but regularly ovulating women found that for every BMI point greater than 29.0, there is a 4% to 5% drop in spontaneous pregnancy rate. Essentially, women with a BMI of 35 had a 26% decreased chance of becoming pregnant compared with women with BMIs between 21 and 29 [91].

Male obesity can lead to erectile dysfunction and cause increased scrotal temperatures, low semen quality, and changes in sperm proteomes, which are all factors that affect male fertility [84; 85]. One study found that as BMI increases, ejaculate volume and sperm motility decrease [93]. Abnormal reproductive hormone levels, including elevated estrogen levels and reduced androgen, inhibin B, and SHBG levels, are thought to ultimately be responsible for decreased total sperm count, concentration, and motility as well as possibly leading to sperm DNA damage [85; 93; 94].

Insulin resistance is a key factor in obesity-related infertility among both sexes [15; 87]. Low SHBG levels and abnormal hormone levels are typically found in individuals with high concentrations of circulating insulin, as with those with poorly controlled diabetes, leading to decreased testosterone levels in men and increased testosterone levels in women [15; 95]. Abnormally high levels of leptin are found in obese individuals, and this may also contribute to the poor regulation of sex hormones [87].

Compounding this problem is the hypogonadal-obesity cycle in men, whereby high levels of body fat (and subsequent increase of aromatase) cause high estrogen and low testosterone production (hypogonadism) and lead to increased deposition of fat. This increases aromatase activity and turns remaining testosterone to estradiol and further inhibits testosterone concentrations, thereby leading to greater fat deposits [12].

It has been proposed that obesity may enhance the toxicity of environmental chemicals known to cause reproductive harm due to retention of toxins in body fat [96]. To date, research has not been conducted on humans. However, an animal study showed that obesity exacerbated the mutagenic effects of one toxin (acrylamide) upon sperm, resulting in 30% fewer implanted embryos in the acrylamide-exposed obese group compared with the exposed lean group [96].

In regard to the HPG axis, men and women differ in that the testes begin to release steroid hormones in utero, whereas the ovaries only begin to synthesize these sex hormones at puberty, during which they are signaled by gonadotropins. The adrenals produce hormones in both sexes before birth [97]. Therefore, childhood obesity has the potential to affect normal reproductive maturation and function before and during puberty, including early puberty, hyperandrogenemia, and PCOS in girls and delayed puberty and hypogonadism in boys [41].

DIABETES

Because type 2 diabetes is closely linked with overweight and obesity, many of the same conditions that reduce fertility in people with excessive weight are found in those with type 2 diabetes or impaired glucose tolerance (i.e., prediabetes).

Patients with type 1 diabetes are also less fertile than their nondiabetic counterparts [98]. As previously discussed, insulin resistance and excessive endogenous insulin, common in individuals with prediabetes and both type 1 and type 2 diabetes, causes low SHBG levels, which in turn creates abnormal concentrations of sex hormones in humans [15; 95; 99]. It has been found that androgen (specifically,

testosterone) levels are significantly reduced and estrogen levels are significantly increased in men with diabetes or prediabetes; the opposite effect is seen in women [15].

Diabetes is known to delay the onset of menarche and hasten the onset of menopause, greatly shortening the finite female reproductive span. Additionally, diabetes can cause oligomenorrhea and secondary amenorrhea [100]. However, tight glycemic control and prevention of disease complications have been proven to increase the regularity of menstruation/ovulation and increase fertility rates to near national averages [100]. Though live birth rates in women with diabetes have increased in the past 20 years due to improved glycemic control and fewer complications, it should be noted that the risk of congenital defects remains higher in women with diabetes [98]. A 1996 study found that established diabetes with poor metabolic control (especially in the pregestational period to 8 weeks' gestation) caused defects in up to 13% of infants; however, a 2010 study found that only women with type 1 diabetes (not type 2) were statistically more likely to have offspring with congenital abnormalities [101; 102].

Men with diabetes typically have decreased sperm counts, increased DNA mutation and fragmentation of sperm, and a higher degree of oxidative stress on sperm than the general population [103]. The advancement of the disease to other conditions, the duration of the disease, and/or poor glycemic control are associated with higher infertility rates among men with diabetes [103]. As with women, tight glycemic control is required to maintain near normal fertility in adult male patients with type 1 and type 2 diabetes and to improve reproductive development in adolescence.

EATING DISORDERS AND EXCESSIVE EXERCISE

Underweight is a significant risk factor for infertility in women, particularly when associated with an eating disorder. It is common for underweight individuals to have poor nutritional status, including low stores of the vitamins, minerals, and antioxidants necessary for proper hormone regulation, metabolism, and protection against oxidative stress from free radicals and other reactive oxygen species.

Lack of adequate fuel intake in women is partially responsible for amenorrhea that can be anorexia-, bulimia-, and/or exercise-induced [104]. It is precisely this lack of metabolic fuel, coupled with depleted stores of body fat, that triggers sensors to cause the body to inhibit the release of gonad-stimulating reproductive hormones, leading to an absence of ovulation and menstrual periods [104]. Research suggests that one of the key hormones required for ovulation is leptin, which is found in fat cells [105; 106]. In athletes, or women who engage in excessive exercise, or anorectics, severely reduced body fat, and therefore leptin levels, combined with physical stress (induced by extreme activities) or emotional stress (due to competition or body image), are responsible for amenorrhea [105]. Studies have shown that supplementation with leptin alone can induce ovulation in amenorrheic women with low BMIs [106].

Recurrent miscarriage is a common problem among bulimic women. However, it does not seem to be induced solely by low pregestational BMI or low gestational weight gain found with other eating disorders [107].

Excessive exercise coupled with caloric restriction can be responsible for hormone deficiencies and subsequent infertility in men but is less common due to male physiology. Oxidative stress upon semen has been shown in patients who exercise excessively [108]. Evidence also supports oxidative stress as a key element in the pathophysiology of varicocele-related infertility [109].

Women younger than 25 years of age generally seek the majority of their health care from obstetricians/gynecologists, and for this reason it is particularly important for these practitioners to screen patients for eating disorders, of which 90% are initiated by 25 years of age [110]. In addition to the potentially life-threatening consequences of anorexia or bulimia to adult women, there are risks to the fetus (e.g., low birth weight, prematurity, miscarriage) [107]. For this reason, it is important to first identify and attempt to treat a patient's eating/exercise disorder prior to initiating fertility treatments. As such, all healthcare professionals are urged to employ a lower index of suspicion for screening their patients than they currently do for underweight infertility patients or patients complaining of amenorrhea [110].

DIET AND NUTRITION

A considerable number of studies indicate, mostly indirectly, that poor diet and inadequate nutrition may be the most important overall factor for male and female fertility status [70; 71; 104; 105; 107; 111; 112]. Although there is a marked lack of research that directly compares diet to fertility outcomes, it stands to reason that if, for example, excessive sugar intake eventually causes insulin resistance, and insulin resistance and high circulating insulin levels can cause infertility, then heavy sugar intake may lead to infertility. Changes in fertility status have been associated with many conditions that can be directly linked to diet, including anorexia, obesity, metabolic syndrome, insulin resistance, and diabetes.

Diets rich in fat, novel sugars, simple carbohydrates, and low-quality protein sources, most of which are vitamin, mineral, and antioxidant poor, create deficiencies in contemporary Americans' nutrition that may lead to, among other conditions, infertility [113]. Obesity- and type 2 diabetes-related infertility are both fundamentally diet and nutrition induced, and other risk factors, such as alcohol and tobacco use, are exacerbated by poor diet. Because certain individuals' bodies are depleted of vitamin, mineral, and antioxidant stores, the ability to counteract even normal metabolic oxidative damage to reproductive organs and processes, let alone the additional stress imparted by toxins, is compromised. Antioxidant cofactors such as zinc, copper, selenium, and manganese are lacking in many individuals.

One study of alcohol consumers compared sperm concentration and motility with vitamins C and E, beta carotene, folate, and zinc intake. The researchers found that those with a higher intake of these compounds had better semen parameters [70]. However, the study may have been skewed by several variables, including participant self-reporting of alcohol and nutrient intake, types of foods cooked, and food preparation technique contributing to variations in nutrient levels [70].

In addition to a poor overall diet, there are certain foods that should likely be avoided when trying to conceive. Soy products (a source of genistein, a phytoestrogen) are thought to affect endocrine function, and while further research is needed in this area, in the interim period, it may be wise for individuals to avoid soy while trying to conceive [114]. Various studies have found that very high intakes of genistein are associated with adverse effects on female reproductive physiology and pregnancy outcomes [113]. High intake of non- or low-fat dairy products may cause anovulatory infertility; it is proposed that changes in milk composition, such as the addition of whey proteins during the fat extraction process, are responsible for increased androgenic effects in women [115]. This finding is from one study alone and warrants further research, as low-fat dairy products are ubiquitous. A 2008 study implicates high intake of animal protein as a factor for ovulatory infertility and suggests replacing meat sources with vegetable protein sources; replacing as little of 5% resulted in a 50% increase in fertility in the high-meat-intake group [116]. When assessing patients for infertility, healthcare professionals should keep in mind that a varied, balanced, and calorie-appropriate diet is especially important to overall health.

PSYCHOLOGICAL FACTORS

There is increasing evidence that psychological stress has a negative effect upon fertility. Both follicle growth and sperm production can be compromised due to the body's adaptive stress response, which negatively influences the reproductive axis of both sexes and can lead to hyperprolactinemia, insulin resistance, and decreased antioxidant cofactors over time [117; 118; 119; 120].

Hyperprolactinemia is a known cause of hypogonadism and anovulatory amenorrhea; one study found that 20 out of 70 women with infertility in a research group had excessive levels of prolactin [120]. Another study, published in 2010, postulates that catecholamines released in response to stress can slow blood flow enough to delay egg implantation in the uterus [121]. The same study found that reduced conception rates coincide with increasing levels of alpha-amylase, but not cortisol, in the female body. These studies add to the abundance of anecdotal evidence that suggests stress contributes to or causes ovulatory infertility.

Psychological factors, such as stress, anxiety, and depression, existing before or as a result of not being able to conceive, are thought to heavily influence the outcome of infertility treatments. Stress and anxiety cause an increased immune response (e.g., high levels of activated T-cells in the peripheral blood), resulting in reduced implantation rates in women undergoing embryo transfer IVF [122]. It has been found that women experience a significant amount of distress during the second and third years of attempts at conception, either naturally or though IVF or other ART treatments [123]. One study of couples undergoing IVF treatment in Turkey found that when detailed explanation of the IVF process, psychological support, and counseling were provided, the success rates more than doubled [33]. However, stress levels can be difficult to accurately quantify; therefore, most studies—as in the Turkish study—use women or couples attending counseling interventions or support groups as an experiment group to compare with those receiving standard care as a control. Because questions about how stressed one felt during the last cycle are subjective and stress is thought to have a similar effect on physiology in both individuals trying to conceive naturally and those undergoing infertility treatment, the results of infertility treatment/stress studies are usually extrapolated to determine that stress is a factor for infertility in the general population.

One notable study did examine couples trying to conceive on their own after experiencing infertility for less than two years and concluded that psychological interventions (e.g., support groups, cognitive-behavioral therapy) significantly increased pregnancy rates [124]. Cognitive-behavioral interventions have shown the potential to effect the greatest improvement in fertility status [123; 124]. Cognitive-behavioral therapy versus fluoxetine 20 mg for infertility stress reduction was evaluated in a 2013 study, the results of which reaffirmed the benefit of psychotherapy for infertility stress [125]. The study identified a chief concern for women experiencing infertility stress: the prospect of facing a life without offspring. Another significant concern was that infertility would lead to divorce. Cognitive-behavioral therapy was particularly beneficial for addressing these concerns. Other issues, including social and sexual concerns, were also improved with psychotherapy; however, sexual concerns were also alleviated in the fluoxetine group.

SEXUALLY TRANSMITTED INFECTIONS

It is estimated that each year there are approximately 1.6 million new cases of gonorrhea and 4 million new cases of chlamydia among American women, with only half of these numbers diagnosed/reported to CDC [126]. Many of these bacterial STIs occur without noticeable symptoms or treatment and can lead to permanent damage (e.g., scarring, adhesions, cysts) of the uterus, fallopian tubes, and surrounding tissues, especially in young women. This damage can impair fertility, even after the infection is resolved.

Chlamydia

Bacterial infection with *C. trachomatis* is normally confined to the lower genital tract, where the cervix serves as a barrier that protects the uterus, fallopian tubes, and ovaries. However, prolonged untreated infections can spread to the upper reproductive tract, and certain practices, such as douching, can cause the infection to ascend and may lead to PID. It is estimated that 10% to 15% of chlamydial infections in women of all age groups will lead to PID [47; 126]. Due to sexual practices, such as failure to use condoms, and biologic factors, such as the cervix not yet being fully mature, adolescent girls have a 10 times greater chance of developing PID after acquiring chlamydia than women 25 years of age or older [47]. An additional risk factor for chlamydia infection and PID is having multiple sex partners [47].

Reinfection with chlamydia, due to the male partner(s) not being properly treated or not knowing which male partner is infected, is a serious concern that greatly elevates the chance of developing chlamydia-related PID and infertility [47; 126]. Chlamydia, like most other STIs, has far greater potential for reproductive harm in women compared with men [47]. It is uncertain whether chlamydial infection is strongly associated with male infertility; however, when seminal chlamydial antibodies were found in men, a significant number of their partners were found to have tubal infertility and/or undiagnosed PID [127].

Gonorrhea and Other STIs

The odds ratio for tubal infertility in women who have had gonorrhea is 2.4 compared with women without any prior STIs. Infection with the trichomoniasis parasite is also associated with tubal infertility (odds ratio: 1.9) [128]. Human papillomavirus (HPV) is not directly responsible for ovulatory infertility or obstructive disorders, but treatments for and complications of the virus can damage the cervix (e.g., reduced cervical mucus, cervical scarring, cervical stenosis after cone biopsy, cervical cancer), causing infertility. Human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) is known to increase the severity of pelvic disease [47].

ALCOHOL USE

Although the results of studies documenting the impact of alcohol intake on reproductive health are mixed, due in part to the under-reporting of use, the general consensus is that consumption negatively affects reproductive potential in a dose-dependent manner. However, it should be noted that couples have anecdotally reported reduced conception at intake levels as low as one drink per week [129]. Among patients undergoing IVF, increased levels of alcohol intake in both men and women lead to higher miscarriage and lower pregnancy and live birth rates, especially when consumption is near to the time of procedures [129].

A study with nearly 5,000 female participants linked increased alcohol consumption to endometriosis and ovulatory infertility. Researchers found that the risk ratio for ovulatory factor infertility was 1.3 for moderate drinkers and 1.6 for heavy drinkers; the risk for endometriosis was found to be about 50% higher in women who consumed any amount of alcohol [130]. A Danish study following 430 couples, 20 to 35 years of age, trying to conceive for the first time found that the odds for becoming pregnant steadily decreased as women's alcohol intake increased [131]. Finally, another study published in 2004 followed 7,393 women over an 18-year period and found that heavy alcohol use was associated with increased likelihood of infertility examinations and primary and secondary infertility [132].

Though these studies seem to indicate a trend of increasing female infertility rates with progressively higher alcohol intake, others have shown less significant negatives up to heavy intake levels or no variation in fertility status relative to alcohol intake [133]. While definitive information and well-designed, large-scale studies about alcohol intake and its relationship to fertility status are lacking, the studies conducted so far often reflect individuals' unwillingness to report their actual drinking habits, especially when it relates to their ability to produce healthy offspring. Therefore, it seems reasonable to assume that the majority of people understand that heavy alcohol use negatively affects general health,

and it may be best to err on the side of caution and advise female patients to drastically limit or cease their intake of alcohol when trying to conceive [131].

The effect of alcohol consumption on male fertility is unclear. Some studies, such as the aforementioned Danish study of 430 couples, have not observed a dose-response relationship between alcohol consumption and ability of men to actually conceive [131; 134]. A group of researchers found no difference between men's average weekly alcohol use and fertility outcomes or semen parameters among male partners in couples attending one United Kingdom infertility clinic [134]. Interestingly, a group of Italian researchers noticed a protective effect of moderate alcohol drinking upon semen, due to "an antioxidant effect of some alcoholic beverages," notably wine [135]. The antioxidant effect of alcoholic beverages, as found in the Italian study, is negligible compared with other sources of these protective compounds, such as unfermented grape juice.

However, the majority of studies have concluded that consumption of alcohol may negatively influence semen quality and sperm motility and cause spermatogenetic disorders in a dose-dependent manner [70; 136; 137; 138]. Notable research on alcohol's effect on spermatogenesis utilized blind interviews with family and friends of participants to gather a more accurate assessment of their alcohol intake levels [136]. It was shown that low alcohol intake caused few negative effects and, somewhat predictably, high intake caused serious spermatogenic pathology. Additionally, the report stressed that consumption of moderate amounts of alcohol may affect semen quality more than previously thought [136]. Additional research is necessary to form a definitive causal relationship and to determine a maximum "safe" limit.

TOBACCO AND CAFFEINE

As of 2020, tobacco (nicotine) and caffeine were the two most commonly used stimulants in the United States. An estimated 80% to 90% of adults and adolescents habitually use caffeine, and 72 million individuals 12 years of age or older use tobacco products [139; 140].

Tobacco Smoking

Numerous studies have concluded that tobacco smoking is a risk factor for infertility in men and women and that nicotine and/or smoking affects reproduction in a dose-dependent manner [70; 71; 129; 137; 138; 141; 142; 143; 144; 145]. In-vitro models have shown that nicotine displays an oxidizing effect on the sperm plasma membrane and sperm DNA, resulting in nonviability [141]. In-vivo research shows that smoking increases seminal reactive oxygen species by more than 100% and, compounding the potential for spermatic damage, decreases seminal plasma concentrations of the antioxidants vitamin E and vitamin C and antioxidant cofactors (e.g., zinc) [70; 146; 147; 148]. It is known that tobacco smoke contains many reactive oxygen species and stable and unstable free radicals, including the highly toxic superoxide anion and hydroxyl radicals. This is in addition to the many carcinogenic, mutagenic, and other toxic chemicals contained in the particulate and gas phase of cigarette smoke [148].

Women who smoke put their reproductive system under increased oxidative stress and suffer the same depletion of antioxidants and unnatural aging as men. On average, menopause begins 1.5 years earlier in women who smoke [71]. It has also been suggested that the effect of smoking on female fertility is similar to a 10-year increase in age [129]. One meta-analysis of 12 studies found that the odds ratio of infertility in female smokers is 1.6 versus nonsmokers, and another meta-analysis of 9 IVF treatment studies found that the odds ratio for becoming pregnant is 0.66 versus nonsmokers [142]. A 2009 meta-analysis of 17 studies on the effects of active

smoking during any ART treatment found that, compared with nonsmokers, the odds ratio for becoming pregnant was 0.56; spontaneous miscarriage, 2.65; and ectopic pregnancy, 15.69 [149]. These risks can be reversed by cessation of smoking [129]. Nicotine alone has been found to disrupt follicular growth, but not vascularization, in human ovarian follicles [145]. Granulosa cell apoptosis increases relative to the dosage of nicotine [145].

While some investigations have focused on nicotine (and/or cotinine, a nicotine metabolite) as the prime component of tobacco products leading to reproductive damage, others have examined the effects of heavy metals, such as cadmium, and other compounds isolated from tobacco smoke. Cadmium, found in soils of tobacco growing regions, is taken up by tobacco plants and highly accumulates in the leaves [150]. One study concluded that cadmium exhibited the potential to negatively affect intrafollicular processes (e.g., oocyte-cumulus expansion) with increasing dosages, as a result of decreased progesterone synthesis and suppression of FSH [143]. A 2010 literature review specifically cites cadmium and polycyclic aromatic hydrocarbons, among the thousands of other components, as responsible for damage to every stage of female reproductive function [151]. High levels of cadmium were found in the semen of male smokers with asthenozoospermia [152]. The synergistic effect of smoking and other environmental toxins, such as asbestos, plasticizers (e.g., phthalates, bisphenol A [BPA]), and diesel and coal particulates, on reproduction has also been noted [143; 144; 148; 151; 153].

Caffeine

Results of studies to determine whether or not caffeine use can lead to infertility are mixed and inconsistent, but as with moderate alcohol use, individuals with infertility are generally advised to limit caffeine intake (especially from coffee) to 100 mg/day. For reference, the caffeine levels of products Americans are most likely to consume are [154]:

- Drip coffee (8 oz.): 96 mg
- Espresso "shot" (1 oz.): 64 mg
- Black tea (8 oz.): 47 mg
- Soft drinks (8 oz.): 22 mg
- "Energy" drinks (8 oz.): 29 mg

A multinational European study published in 1997 concluded that 500 mg/day or more of caffeine significantly increased the odds of subfecundity for women who had never conceived; the odds ratio was even higher for concurrent smokers [155]. This study also showed an 11% increase in time to first pregnancy among those who consumed caffeine [155]. A Danish study published one year later found that, compared with women consuming 300 mg of caffeine per day or less, those consuming 300–700 mg of caffeine per day had a fecundability odds ratio of 0.88 per cycle; for those consuming in excess of 700 mg of caffeine per day the ratio further declined to 0.63. Similar numbers were seen in men as well [156].

Female coffee drinkers have been found to have more infertility problems compared with those who consumed other sources of caffeine (e.g., tea, chocolate, colas) [156]. The conclusion that the caffeine in coffee has the greatest impact on fertility in women is supported by at least one other study; incidentally, the same study also found that men who drink tea heavily are more likely to be infertile [157]. The mechanism of how caffeine affects fertility is not clear, but it is thought that the alkaloid may alter hormone levels. In fact, a Japanese study found that caffeine elevates SHBG and estradiol levels in women [112; 158]. Elevated estradiol levels (70% greater) were also found during the early follicular phase in women consuming 500 mg/day compared with a 100 mg/day intake group [159].

On the other hand, some research has shown that caffeine intake is not a significant factor for infertility in women [160; 161; 162; 163]. A 2009 study concluded that while high soft drink intake is a risk factor for ovulatory disorder infertility, caffeinated sodas were no more likely to cause ovulation irregularities than noncaffeinated types [160]. A separate study found that although menstrual cycles tend to be shorter, women who are heavy caffeine consumers are no more likely to have an anovulatory episode, short luteal phase, long follicular phase, or long cycle. The shorter total cycle duration was due to short menses, attributable to vasoconstriction [161]. Another group of researchers found that there was no increase in length of time to conception between women with caffeine intake levels of 500 mg and 7,000 mg per month [162]. Yet another study found that caffeine only negatively affected the probability of conception when used concurrently with alcohol [163].

It has been suggested that research regarding caffeine and fertility may be biased due to self-reporting of use and the retrospective collection of data on consumption, in some cases as much as six years later [112]. One well-designed study, in particular, addressed this concern by interviewing participants at three-month intervals and concluded that women who drank 1 cup or less of coffee per day were twice as likely to become pregnant than those who drank more and that increased intake inversely correlated with conception rates [164]. However, another well-designed study, in which women reported their intakes monthly, found that no source or amount of caffeine influenced fertility outcomes except tea; one-half cup or more of tea per day doubled the chances of conception each cycle [165].

In spite of these mixed results, it is generally recommended that women who wish to become pregnant begin to reduce caffeine intake, as the substance crosses the placenta and has been shown to affect fetal development and gestation (e.g., birth defects, premature labor, preterm delivery, low-birth weight offspring) in animals [166]. Although human studies have been inconclusive, it should be noted that caffeine causes increased blood pressure, dehydration, and changes in fetal sleep pattern and that the fetus is not adept at metabolizing the stimulant.

CONTROLLED SUBSTANCE USE

Cannabis

Cannabis is by far the most commonly used recreational drug in the United States, with an estimated 31.6 million regular (past month) users 12 years of age or older in 2019. Its use increased from 22.2 million users in 2015, and its popularity is rising [139; 167]. Knowledge of how the drug affects fertility is also increasing.

The action of cannabis's primary active components, delta-9-tetrahydrocannabinol (THC), cannabidiol, and cannabinol, upon fertility and reproduction was unknown before the discovery of cannabinoid receptors in 1988 and the unraveling of the mammalian endocannabinoid system in the 1990s. It is now thought that cannabinoids influence many reproductive processes, including hormone regulation; oocyte production; sperm production, motility, and capacitation; sperm-oviduct interactions; acrosome reactions; embryo oviductal transport; blastocyst implantation; post-implantation embryonic growth; and placental development [16; 17; 18; 20; 168]. Any variation in these processes can lead to infertility. Animal research has identified several structures previously thought to be regulated only by hormones that are at least partially regulated or signaled by the endocannabinoid system [19; 20].

The perception that cannabis has no deleterious effects is perpetuated in popular culture. With a number of U.S. states allowing its sale for medicinal and recreational use and growing knowledge of cannabinoid therapy, a belief in cannabis as a cure-all flourishes in some circles. While the drug and its synthetic derivatives do undoubtedly offer promise as therapeutic agents for certain conditions, reproductive detriment can befall those who abuse cannabis (or partake moderately) or even those who may be taking a cannabinoid obesity drug.

Results of studies regarding the outcome of recreational cannabis use upon human reproduction show primarily ill effects. For example, many of the same negative reproductive effects of tobacco smoking, such as oxidative damage and a decrease in antioxidant levels, are caused by smoking cannabis as well. Cannabis smoke contains many of the same harmful and/or carcinogenic compounds as cigarette smoke (e.g., polycyclic aromatic hydrocarbons, ammonia, hydrogen cyanide, nitrogen oxides), and some are found in much higher levels than in cigarette smoke. Ammonia is present in both mainstream and sidestream cannabis smoke in concentrations 20 times greater than in tobacco smoke [169]. Certain studies have also linked cannabis use with testicular germ cell tumors [170].

In addition to cellular damage caused by oxidation and toxins, several studies have linked cannabis use with increased odds of ovulatory factor infertility, early loss of pregnancy, and decreased semen parameters [19; 171; 172; 173; 174]. Researchers found that the risk ratio for abnormal ovulation in women who had used cannabis within the same year of trying to conceive was 2.1, and for those who had stopped using the drug more than one year prior to attempting pregnancy, the risk factor was 1.7 [171]. Occasional cannabis users (defined as using less than three times in three months) have been found to have a follicular phase 3.5 days longer on average than non-users; interestingly, heavy users (more than three times in three months) had only a two-day increase [174]. Long follicular phase, causing ovulatory delay or inhibition, is associated with infertility and miscarriage.

One longitudinal study found no impact of cannabis use on sperm concentrations [175]. However, sperm motility may be impacted by cannabis use, as are straight-line velocity, average path velocity, and acrosome reactions [173; 176]. These impaired sperm are likely unable to fertilize an egg, and if one happens to achieve success, the embryo is at great risk of being nonviable. One study posits that sperm propulsion is affected by cannabis use because THC mimics anandamide, an endocannabinoid responsible for opening Hv1 channels in sperm flagella; excessive cannabinoid causes the channels to open prematurely and the sperm to "burn out" before reaching the ovum [177]. A 2013 study found that seminal plasma levels of anandamide are significantly reduced in men with asthenospermia and oligoasthenoteratospermia (i.e., oligospermia, asthenospermia, and teratospermia combined) [168]. Thus, it appears that anandamide and other cannabinoid levels must not be too high or too low for optimal reproductive potential.

In light of the relatively new discovery of the endocannabinoid system, research suggests that a carefully balanced endogenous cannabinoid system, which is involved in regulation and signaling of reproductive processes, plays an important role in reproduction [168]. A disruption of this delicate balance by exocannabinoids, or even a lack of certain endocannabinoids, can greatly decrease the likelihood of conception, as cannabinoid receptor expression has been identified in reproductive tissues in the testes, uterus, and endometrium and in sperm and ova [19; 20; 168]. Though the endocannabinoid system is still poorly understood, it appears that tailored exocannabinoid therapy may be a new frontier in fertility treatment and/or contraception [19; 168; 176].

Cocaine

Use of cocaine is known to cause low sperm concentration and motility [178]. One study showed that men who used cocaine within the previous two years had a high risk for low sperm count. Chronic users (more than five years) had an increased risk for low sperm count and motility and malformed sperm.

Cocaine use is also strongly associated with tubal infertility. Fallopian tube abnormities are 11 times more likely in women who have used this drug [171]. Although no studies have assessed the impact of cocaine on human ovulatory function, heavy cocaine use has been shown to inhibit the release of LH in animal studies. This, in theory, could cause anovulation; however, one study found that cocaine use is not significantly associated with ovulatory infertility [171].

Heroin and Opioids

In one small scale study, 93% of heroin addicts had abnormal semen parameters [179]. Among these men, problems with motility were the most common finding (78%), followed by mutated sperm (28%) and low sperm concentration (16%). Heroin abuse can lead to lowered levels of hormones necessary for proper male gonad function, including LH and testosterone [180]. Lower than normal LH, FSH, and progesterone have been found to be responsible for ovulatory factor infertility in women addicted to heroin [181]. Additionally, heroin has been shown to affect the HPA axis in humans [180; 182]. It should be noted that these effects are expected with the use of other opioids as well, including the prescription drugs oxycodone, fentanyl, and morphine.

Methamphetamine

There are very few studies that have examined the effects of methamphetamine use on human reproduction and specifically on fertility status. It is certain that methamphetamine places the reproductive organs under extreme oxidative stress and causes metabolic distress [183]. Regular methamphetamine users often become severely malnourished and typically consume a large portion of their calories from sugar and carbohydrates. The same prognosis for infertility as those with poor diet, eating disorders, and possibly insulin resistance is to be expected in these individuals.

Available data from animal studies shows a high level of sperm DNA fragmentation and a diminished ability to contribute to conception in men who are heavy methamphetamine users [184]. Another animal study conducted in 2002 found a dose-dependent increase in terminal deoxyuridine triphosphate nick-end labeling-positive cells in the seminiferous tubules of the testes, indicating apoptosis [185].

Androgenic Anabolic Steroids

The use of androgenic anabolic steroids (testosterone derivatives) among amateur and professional athletes and bodybuilders is known to contribute to or cause infertility by interfering with the body's endogenous production of hormones and causing hypogonadotrophic hypogonadism [186]. Gonadotropin secretion is suppressed in users, who are typically male, due to the artificial negative feedback induced by testosterone analogues (10 to 40 times higher than normal levels). Low gonadotropin causes low FSH and LH and consequently a drastic reduction in spermatogenesis. Testosterone preparations similar to certain androgenic anabolic steroids have been studied as possible male contraceptives due this same effect.

PRESCRIPTION DRUGS AND THERAPEUTIC EXPOSURES

Many prescription medications have been shown to impede fertility via a wide range of activities, including gonadal toxic effects, altering the HPG axis, and impairing sperm transportation [187]. Certain medications may impair fertility in more than one way. Although some of the most common medications affecting male fertility will be discussed in this section, a listing of all drugs affecting fertility is beyond the scope of this course.

Antibiotics of several different classes have been shown to affect sperm, including tetracycline, neomycin, erythromycin, gentamicin, and nitrofurantoin [187]. This may also affect treatment choices, as these antibiotics may be used to treat existing infections that affect fertility, including *C. trachomatis* and *N. gonorrhoeae*. Medications used for a variety of conditions have been associated with impaired erectile and/or ejaculatory function, including beta blockers (e.g., propranolol), tamsulosin, and alpha blockers [187; 188; 189; 190; 191]. Use of serotonin reuptake inhibitors and other antidepressants can severely affect libido and may result in anorgasmia. Other medications, particularly those used to interfere with hormone regulation or production (e.g., exogenous testosterone, GnRH agonists, and

spironolactone) can inhibit the HPG axis, decreasing testosterone synthesis [187]. Finally, other medications, including cimetidine, sulfasalazine, colchicine, and allopurinol, can impair semen parameters or fertilization [187].

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

In recent decades, the increased incidence of endocrine-related diseases has led to an examination of the growing number of potential environmental sources of endocrine-disrupting chemicals. Many heavy metals and chemicals found in occupational, home, and natural environments are endocrine disrupters, but others are mutagens. Both have the potential to cause infertility. Additionally, occupations that expose workers to prolonged elevated temperatures are a risk factor for infertility.

Many endocrine-disrupting chemicals are consumed or absorbed indirectly. For instance, methylmercury, a known endocrine disrupter, can leach into waterways from abandoned mines and eventually into fish that may be consumed by humans. Other endocrine-disrupting chemical exposures are direct, such as the inhalation of solder vapors in electronics assembly plants or anesthetic gases in medical settings. The list of potential infertility-causing toxins is extensive, including, but not limited to [192; 193]:

- Alkylmercury
- Antimonide
- Boron
- Cadmium
- Carbon disulfide
- Chlordecone
- Chloroprene
- Some carbamates (e.g., carbaryl)
- Diaminostilbene
- 1,2-dibromo-3-chloropropane
- Ethylene glycol ethers
- Ethylene dibromide
- Inorganic lead
- Manganese
- Methyl chloride
- Organic solvents
- Synthetic estrogens and progestins
- Tetraethyl lead
- Combined exposure to styrene and acetone
- Vinyl chloride
- Welding operations (fumes)
- Certain pesticides (e.g., carbamates and organophosphates, both commonly used in agriculture and at home)

Although there is a wide array of potentially harmful environmental factors, a few of the most common and most harmful factors will be discussed here.

One study found that male laundry workers exposed to the dry cleaning solvent perchloroethylene (perc) were more than twice as likely to be infertile compared with men with no such exposure [194]. Another study found that women working in the laundry industry exposed to perc or whose husbands were exposed to perc were more likely to experience spontaneous abortion [195]. However, because both these studies involved the laundry industry, there was a possibility that exposure to excessive heat was a factor. Prolonged heat exposure is known to cause both a reduction in sperm concentration and an increased risk for spontaneous abortion [192].

Perfluorinated chemicals are a class of compounds used in many household products, including clothing, upholstery, carpets, wrapping paper, nonstick cookware, personal care items, and pesticides. There is evidence that these chemicals cause endocrine disruption, ovulatory disorders, infertility, and spontaneous early abortion in humans at blood plasma levels common in industrialized nations. Higher rates of exposure (i.e., twice the amount found in the general population) are most strongly associated with negative effects [196].

Plastics are ubiquitous today, and phthalates, a class of plasticizer chemicals used to make certain types of plastics more flexible (mainly polyvinyl chloride), are known endocrine disruptors, mutagens, and teratogens [197; 198; 199]. Exposure to phthalate esters occurs on a daily basis for most individuals in the United States starting at a young age, from the home (e.g., in pacifiers, toys, water pipes, perfumes, cosmetics, vinyl flooring, shower curtains, and raincoats) to the hospital (e.g., in intravenous systems, breathing tubes and oxygen lines, and drainage catheters). Documented effects of phthalates are mainly anti-androgenic, causing damage to the testes and sperm [197]. Data on the effects of phthalates on female reproduction are scarce; however, endocrine disruption is unlikely in levels typically found in humans [199; 200].

BPA, another chemical in certain plastics, has gained a reputation for its apparent ill effects, including reproductive toxicity. Two studies published in 2010 support this association. One study of men selected from infertility clinics found that there was an inverse relationship between concentrations of BPA in urine and free androgen index (ratio of testosterone to SHBG), estradiol, and TSH [201]. The second study found that the majority of women undergoing IVF treatments had detectable levels of BPA in their urine and concluded that BPA was inversely associated with peak oestradiol levels and number of oocytes retrieved [202]. BPA has also been linked to recurrent miscarriage [203]. Common sources of BPA are plastic water bottles (which can increase urinary concentrations two-thirds in just one week of normal use), canned food, and reusable plastic food storage containers, which leach BPA at much greater concentrations when the plastic is heated (as a result of filling soon after cooking or microwave reheating) [204].

DIAGNOSING INFERTILITY

Couples who present with fertility issues and who meet the criteria for a diagnosis of infertility (rather than subfertility) will require an infertility work-up. The first step is a complete history, physical examination, and semen analysis [205; 206]. Educational materials stressing lifestyle changes and preconception counseling are also appropriate at this point. Patients may be referred to therapy or counseling to address the unique stresses associated with infertility.

The findings of the history and physical will guide the diagnosis process for both men and women. Aside from issues inherent in the female or male partner, it is also important to consider couples' infertility factor, which is influenced by sexual dysfunction issues and frequency and timing of intercourse [205].

FEMALE-FACTOR INFERTILITY

Women who are older than 35 years of age should be screened for day 3 FSH and estradiol [205]. If the findings of these tests are abnormal, the patient should be referred to an infertility specialist. If the findings are normal or if the patient is younger than 35 years of age, history and physical signs or symptoms (if present) will be the guiding forces to explore the etiology of the infertility. Further testing is usually required and may include a hormonal work-up, hysterosalpingogram, basal body temperature (for three cycles), and assessment of TSH, prolactin, FSH, and estradiol levels [205]. In many cases, laparoscopic infertility evaluations are a final diagnostic procedure. Laparoscopy may be considered for women with suspected endometriosis or histories suggestive of anatomic factors affecting fertility in the presence of normal hysterosalpingogram findings [205].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the American College of Radiology, fluoroscopic hysterosalpingography may be appropriate in the diagnostic workup of patients with infertility and a history or clinical suspicion of endometriosis.

(https://acsearch.acr.org/docs/3093336/Narrative. Last accessed June 16, 2023.)

Strength of Recommendation: May be appropriate

MALE-FACTOR INFERTILITY

For men with abnormal semen parameters, the physical exam should include an evaluation of the prostate and the scrotal contents, which would assess testicular size and consistency, epididymis, vas deferens, and varicocele [205; 206]. Other considerations are body mass, hair distribution, and penile abnormalities. If the initial semen analysis is normal, this indicates that the infertility is most likely due to a female infertility factor [205; 206]. Even in these cases, another semen analysis should be completed if pregnancy has not occurred after four months and again after five months. If the semen analysis returns with abnormal findings, additional testing is necessary. The first consideration should be of exposure to gonadotoxins, including [207]:

- Tobacco smoke or nicotine
- Anabolic steroids
- High levels of alcohol intake
- Antiandrogens
- Hyperthermia
- Environmental toxins (e.g., heavy metals, radiation, pesticides)
- Illicit drugs (e.g., cocaine, cannabis)
- Certain prescription drugs (e.g., chemotherapy, allopurinol, ketoconazole, tetracycline, cyclosporine, erythromycin, sulfasalazine)

If the patient reports exposure to one of these gonadotoxins, semen analysis should be repeated every three months and intercourse should be continued [205]. Another consideration, particularly if the patient reports no exposure to these substances, is the presence of infection. If symptoms of infection are present, this should be treated and, if appropriate, the female partner may be treated as well.

For patients with signs of oligozoospermia, a morning sample of FSH, testosterone, and prolactin will be necessary [205; 206]. These patients should be referred to a male infertility specialist for further diagnostic and treatment options. Some patients will benefit from more intensive tests (e.g., transrectal ultrasonography, scrotal ultrasonography, vasography, or biopsies), but an estimated 70% of male infertility cases may be explained by history, physical exam, and semen analysis [208].

TREATMENT OF INFERTILITY

In many instances, lifestyle interventions can be prescribed that will lead to successful conception; however, in some cases, patients may be unwilling or unable to achieve results through lifestyle change alone. Ovulation and spermatogenesis disorders are often treatable through the identification and treatment of underlying risk factors, including high BMI (e.g., diet and exercise), low BMI (e.g., eating more and exercising less), improved nutrition, stress reduction, and cessation of tobacco, alcohol, and certain drug use. If lifestyle changes fail to improve natural fertility, medications offer some success in natural conception.

LIFESTYLE MODIFICATION TO IMPROVE THE CHANCE OF NATURAL CONCEPTION

Weight Loss

Weight loss and exercise has been proven to greatly improve fertility in anovulatory overweight and obese women [45; 83; 87; 209]. One study demonstrated that in as few as six months, 12 out of 13 anovulatory women on an exercise/calorie-restriction program (with an average weight loss of 14 pounds) resumed normal ovulation and 11 became pregnant. None of the women in the comparison group (who did not complete the six-month program) showed any positive changes in fertility indicators or pregnancy status [83]. Other research has shown improvements in regular ovulation and reduced biochemical abnormalities after a total weight loss of 5% [87]. Morbidly obese women should be warned of the pregnancy risks associated with extreme obesity and encouraged to lose a substantial amount of weight before attempting to conceive [209].

Likewise, BMI reduction in men is crucial to the restoration of normal hormone levels, spermatogenesis, and semen parameters [84]. Natural weight loss is attainable for many individuals who are overweight and slightly obese, but for individuals who are obese and morbidly obese, breaking the hypogonadal-obesity cycle can be extremely challenging without medical interventions (e.g., bariatric surgery, testosterone replacement therapy).

Based on guidelines set by the CDC, patients suspected to have obesity-related infertility should try to achieve at least 150 minutes of moderate-intensity aerobic exercise per week and muscle-strengthening exercise that works every major muscle group at least two times per week [210]. A reduced-calorie diet is also paramount for those wishing to reduce their BMI. Individuals should limit their total daily calories, based on their height and a normal BMI. Replacing fat and sugar calories with vegetables, whole grains, and other sources of fiber is also recommended.

As previously discussed, non- or low-fat dairy products may aggravate infertility in women with high BMIs and should not be recommended to replace full- or condensed-fat dairy products. For the time being, animal protein sources should not be replaced with soy proteins but should instead be replaced with other vegetable proteins. Additionally, a weight-loss support or counseling program should be recommended. Lifestyle modification is extremely important in this group of patients because even IVF and ART treatments have little chance of success in anovulatory women with a BMI greater than 29 [88; 90; 91].

Weight Gain

Naturally restoring normal ovulation and menstrual periods for women with low body fat stores can be particularly difficult to accomplish unless the patient is willing to address the source of the problem. Women with eating disorders or exercise-induced amenorrhea are almost certainly aware of the irregularity or lack of menstruation. However, these patients may be seeking a medical approach to fertility or, rarely, may not have made the connection between amenorrhea and infertility. As discussed, it is particularly important not to inadvertently help this group of women become more fertile without first attempting to treat their low BMI (i.e., less than 19) due to self-health and gestational risks [45; 110].

Many female athletes and women who engage in extreme levels of exercise are goal oriented. For these women, emphasizing achieving the goals of temporarily gaining weight, becoming pregnant, and delivering a healthy child may be met with more acceptance than in eating disordered women. Furthermore, athletes are often cognizant of their physical condition and may be less resistant to weight gain. For other women, the initial patient interaction may be the best chance for meaningful discourse relating to low-BMI-related infertility. Remember that the eating disorder may have been in place since adolescence or earlier and the desire to become pregnant may not be as strong as the desire

to stay thin; avoid giving in-depth lectures on etiology [211]. Refrain from making referrals initially, and instead set a goal of gaining a few pounds in one month to assess ovulatory function. Explain that weight gain and resumption of normal menstruation is the overall safest method of conception and that low BMI extends risks to the fetus, such as low birth weight and premature delivery.

Recommend a temporary eating plan that involves three meals a day without calorie counting, and explain that soy and non- or low-fat dairy products may contribute to infertility; switching to whole milk products is advisable in this case [114; 115]. For extreme exercisers, stress the importance of cutting back on workout frequency, duration, and intensity. Coffee is often consumed by those who exercise excessively; recommend switching to tea or quitting altogether [165]. Again, emphasize the goal of resuming normal menstruation and the idea that even medical approaches to infertility rely on overall health, including proper nutrient levels from foods.

Enhanced Nutrition

Nutritional factors preventing optimum fertility usually accompany other diseases and conditions, including alcoholism, smoking, drug use, obesity, diabetes, and eating disorders. Identifying and addressing these primary risk factors is obviously paramount; however, recommendations of proper diet to infertility patients should be included in all courses of treatment. Specifically, diets rich in food sources of vitamins, minerals, and other antioxidants should be recommended, along with the addition of a multivitamin. This can help the body and reproductive tissues to repair and protect against oxidative damage and reactive oxygen species. As always, a rundown of foods to avoid while attempting to conceive should be given. A proper meal plan should be discussed, and patient education should focus on eating a variety of different foods (especially vegetables) while cutting back on simple sugars, carbohydrates, and fats.

Smoking Cessation

If a patient is a current smoker, he or she should be advised to quit. Reproductive damage caused by smoking has been shown to be mostly reversible upon cessation in both men and women, but the time to pregnancy is increased [129]. It is estimated that the effects of smoking upon sperm production and other male reproductive factors can be reversed within one year of cessation, and based on results from women undergoing IVF treatments, the same approximate time frame is expected for recovery of the female reproductive system [129; 144]. After approximately one year of not smoking, the odds ratios for spontaneous miscarriage and ectopic pregnancy also return to near normal [129; 149].

Cessation of Alcohol and Illicit Drug Use

The results of one study showed a "very fast and drastic improvement" in semen characteristics following alcohol withdrawal in chronic heavy users [135]. Male research participants were followed over a six-year period of continued alcohol abuse, during which their condition steadily worsened from teratozoospermia to azoospermia. Upon cessation of alcohol use, semen parameters returned to normal within three months [135]. This study illustrates one of the fundamental lifestyle changes that can be implemented to improve outcomes of male factor infertility, and while alcoholics are an obvious extreme, most research suggests that low-to-moderate users with infertility will also benefit from abstaining from alcohol use. Additionally, there are far fewer congenital defects in infants whose fathers abstain from alcohol at least two months before and during conception as spermatogenesis takes approximately 60 days [135]. Because drinking alcohol during pregnancy is strongly discouraged in general, women who are trying to conceive should also be advised to stop drinking for a similar time frame to allow hormone levels to normalize and oxidative damage upon oocytes to cease.

Certain illicit drugs leave a lasting effect on the reproductive organs that no lifestyle change will mitigate. Heavy and prolonged cocaine use in women, for example, severely damages the fallopian tubes, from which there may be no reversal. Male reproductive damage from chronic, heavy cocaine use is also permanent in most cases. The best initial course of treatment would be for ex-addicts to eliminate all other sources of oxidative damage from their lives and to switch to a diet rich in vitamins, minerals, and antioxidants, but referral to an assisted reproductive specialist is probably in order. Occasional users (of all illegal narcotics) should be advised to quit several months before trying to conceive to lessen the chances of miscarriage and congenital defects.

For recovering heroin users, methadone treatment will not restore normal ovulation in all women, though it may help for some [212]. Before attempting to conceive, it is best to be opiate-free (including methadone) for several months, for the sake of the fetus and to allow the body to normalize. It appears that cessation of use is also the only way to restore some degree of fertility for men, but heroin has been shown to cause permanent male reproductive damage [33]. Semen parameters of a methadone treatment group were measured against heroin-user and non-user controls in one study; testosterone levels and sperm motility were actually lower in methadone users than in both of the controls [213]. Ex-heroin users experiencing infertility should be referred to specialists.

Cannabis use is not associated with lasting damage to the reproductive organs, so cessation of use will typically restore ovulation and normal semen parameters. A restoration time frame similar to tobacco smoking cessation is likely in these patients.

Cessation of Anabolic Steroid Use

Based on testing of steroidal male contraceptives, the impact on spermatogenesis can usually be reversed after about one year of cessation of steroid use. However, anabolic steroids used for muscle development are typically taken in dosages 40 times higher than therapeutic contraceptive dosages, so the recovery time may be lengthened [214]. Nonetheless, men have successfully fathered children within two years of quitting steroids [186]. Of course, in chronic heavy users, fertility may be permanently impaired.

Modifying Prescription Drug Use

As discussed, there are several prescription medications that can interfere with fertility and hormone homeostasis. Identification of the drug(s) affecting fertility and cessation of use will usually restore fertility. Of course, not all medications can be discontinued, and the benefits and risks of eliminating any medication should be discussed with the patient and the healthcare team. If necessary, some medications may be tapered down slowly.

Psychological Stress Reduction

Studies have shown that stress reduction has the potential to markedly improve fertility outcomes due to the associated reduction of biochemical anomalies [117; 118; 119; 121; 123; 124]. The American Medical Association has suggested the following approaches for patients to cope with stress [215]:

- Avoid situations that cause stress.
- Incorporate some type of exercise into each day.
- Eat a healthful diet rich in fruits, vegetables, and whole grains.
- Do not smoke.
- Use alcohol only in moderation.
- Quiet time, meditation, prayer, reading, yoga, and relaxation techniques (including biofeedback) can help in stress management.
- Family and friends can provide needed support. Talking about problems can help to reduce conflict and express feelings.

Infertility patients also seem to benefit from psychological interventions, such as support groups and cognitive-behavioral therapy, though the latter has effected superior improvements in fertility status [123; 124]. It is recommended that this information be shared with patients and referrals be made to cognitive-behavioral specialists if patients seem especially frustrated or distressed.

Exercise

Along with proper nutrition, the most important lifestyle change that most Americans would benefit from is the initiation of regular exercise. In addition to providing cardiovascular benefits and protection from other infertility cofactors, such as diabetes, obesity, psychological stress, depression, and hypertension, moderate exercise directly improves sexual and reproductive health [112]. In women with PCOS, the foremost recommendation for restoring regular ovulation and achieving pregnancy is weight loss and regular exercise along with other lifestyle modifications (e.g., improved diet) [209].

As noted, the CDC recommends 150 minutes of medium-intensity aerobic exercise per week and muscle strengthening exercise at least two times per week for moderate health benefits. For greater health benefits, 150 minutes per week of high-intensity exercise or 300 minutes per week of medium-intensity aerobic exercise is recommended, in addition to strength training [210].

Identification of Environmental Toxins and Occupational Exposure

Unexplained infertility may be due to one (or more) of thousands of toxic exposures, which may or may not be avoidable or practical to avoid as a result of where the patient lives or is employed. When there are no easily identifiable risk factors for infertility, inquiry should be made about the individual's occupation. Because many reproductive toxins are endocrine disruptors, symptoms of an endocrine disorder may be present and hormone testing will often reveal abnormalities. Suspicion of endocrine disruption in the absence of other risk factors (e.g., obesity, underweight, cannabis use) warrants referral to a reproductive endocrinologist.

Modification of Sexual Habits

For most couples, having unprotected sex two to three times per week will lead to pregnancy. Because good quality sperm survives in healthy fallopian tubes for up to seven days, under these circumstances, chances are good that the timing of ovulation will occur when there is live sperm available for fertilization.

To a certain extent, timing is crucial. Ideal timing for sex is just one or two days before ovulation; however, variations in cycles, due to stress, nutrition, and other causes, can make predicting ovulation difficult. Techniques to monitor ovulation include recording menstrual cycles on a calendar; checking cervical mucus, position, and/or firmness; tracking basal body temperature; and using ovulation predictor kits [200]. Basal body temperature monitoring is useful for tracking patterns of temperature increase that indicate ovulation and estimating future ovulation dates, but it often indicates ovulation too late and can be too subtle to be effective in one-cycle conception assistance. Cervical mucus consistency is a very good indicator of impending ovulation, but reading can be subjective, as can other methods of cervical monitoring. These techniques can be taught to patients and will lead to some increased success. However, the best advice is often to recommend having sex every day (or every other day) starting just after the last day of menstruation [200]. There is no evidence that any sex positions are better for conception or that retaining ejaculate inside the vagina after intercourse increases pregnancy odds.

If and when normal sexual intercourse fails to produce pregnancy, other interventions are available to treat infertility. However, along with these interventions come side effects, increased health risks (to the parents, fetus, and child), and often a high financial burden [216]. Therefore, whenever feasible, lifestyle interventions should be the first treatment choice, as they usually improve the patients' overall health, energy level, and ability to produce healthy offspring.

Counseling Non-English-Proficient Patients

Communication with couples regarding lifestyle changes is a vital step in improving the chances of natural conception. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter should be utilized. Frequently, this may be easier said than done, as there may be institutional and/or patient barriers.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. When providing care for patients for whom English is a second language, the consideration of the use of an interpreter and/or patient education materials in their native language may improve patient understanding and outcomes.

PHARMACOTHERAPY

With the exception of obstructive disorders, many types of infertility or conditions causing infertility not responsive to lifestyle changes can be treated with medications.

Female Infertility

Ovulatory Disorders

The primary pharmacotherapy for anovulation is the oral antiestrogen clomiphene citrate [45]. For women resistant to clomiphene, second-line therapies include clomiphene plus metformin or gonadotropins. Risks of these endocrine therapies are multiple pregnancies and becoming pregnant; therefore, other health concerns should be evaluated and addressed before beginning treatment. Dopamine agonists (e.g., bromocriptine) can be prescribed for women with hyperprolactinemia-related ovulatory disorders [45].

Endometriosis

Initial therapies for endometriosis include oral contraceptives (progestins and combined estrogen-progestin therapy), GnRH agonists/antagonists, aromatase inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs). Medications used for this condition inhibit ovulation and therefore cannot be considered direct fertility treatments; there is also no solid evidence that medical treatment of endometriosis improves fertility [53]. Only surgical approaches to treatment are completely effective in regaining fertility.

A three-month course of a GnRH agonist is recommended if the condition is unresponsive to the previous treatments; however, it has been found that if medication therapy is stopped, the condition will become worse [217]. Danazol may be prescribed for endometriosis (with good reduction of symptoms and morbidity), but serious negative side effects appear in up to 80% of those taking the drug, causing many to abandon this therapy. Additionally, it can cause harm to a fetus, so administration to those trying to conceive is not recommended.

PCOS

To date, there are no medications approved by the U.S. Food and Drug Administration for the treatment of PCOS; however, several medications are used off label. Clomiphene, an oral antiestrogen medication, has been a mainstay for ovulation induction in women with PCOS; unfortunately, up to 15% of cases do not respond to clomiphene therapy and about 50% of those responding do not lead to increased pregnancy rates [218]. Many studies have tried to prove that combination therapy with the diabetes drug metformin can improve the efficacy of clomiphene, especially in women with BMIs less than 25 who do not have diabetes. However, the results of these studies have been mixed. Nonetheless, metformin is currently recommended for the treatment of hyperinsulinemia, type 2 diabetes, and hyperandrogenism in patients with PCOS and may improve pregnancy rates but not necessarily live births [217]. Treatment guidelines have continually

indicated combination clomiphene/metformin as primary therapy for these women [45; 217]. A 2015 meta-analysis comparing the use of letrozole (an aromatase inhibitor) to clomiphene for ovulation induction found a significant increase in pregnancy and live birth rates with letrozole; some are predicting that letrozole will replace clomiphene as the first-line ovulation induction therapy for women with PCOS [219; 220; 221]. Combination clomiphene/metformin therapy remains preferred for certain patient subgroups.

Gonadotropin therapy, such as with human menopausal gonadotropin (hMG) (a combination of LH and FSH isolated from the urine of postmenopausal women), is an option as an effective second-line approach to treating PCOS. However, use comes with an increased chance of serious side effects and multiple births. One particularly negative side effect of gonadotropin therapy is ovarian hyperstimulation syndrome, which causes excessive follicles to grow simultaneously, possibly leading to kidney failure, blood clots, fluid build-up in the abdomen or chest, or severe electrolyte imbalance if pregnancy is achieved. Cheng et al. have shown a pregnancy rate of 43.3% (compared with 20% in the placebo group) when metformin was combined with clomiphene and hMG in a study of women with PCOS [222]. In 2000, a systematic review of gonadotropin therapy in women with PCOS found that the data were limited and inconclusive to support its use [218]. The review was withdrawn in 2015 [223].

There is fairly strong evidence that the contraceptive medroxyprogesterone acetate is useful for restoring menstrual regularity and menses in women with PCOS [217]. Combination oral contraceptives are not recommended as a first line of therapy, due to their negative influence on insulin sensitivity, but they do offer some benefits, including prevention of endometrial hyperplasia, reduction of endometrial cancer risk, and possibly improved lipid levels [217; 218]. However, because medroxyprogesterone acetate is a contraceptive, it cannot be considered an infertility treatment. Use should be identified, evaluated, and halted in women who wish to become pregnant, especially due to the length of time it takes for medroxyprogesterone (particularly parenterally administered doses) to leave the system.

STIs and PID

The two major STIs responsible for causing PID and infertility—chlamydia and gonorrhea—are treatable with antibiotics, as are other bacterial infections. However, the damage caused by these infections can be much more difficult or even impossible to reverse. Treatment of PID should include broad-spectrum antibiotics capable of killing both *N. gonorrhoeae* and *C. trachomatis*, as endocervical testing can return false negatives. Inpatient treatment may be required for some patients [224]. Hospital-based therapy is suggested when [224]:

- Surgical emergencies (e.g., appendicitis) cannot be excluded.
- The patient is pregnant.
- The patient does not respond clinically to oral antimicrobial therapy.
- The patient is unable to follow or tolerate an outpatient oral antimicrobial regimen.
- The patient has severe illness, nausea and vomiting, or high fever.
- The patient has a tubo-ovarian abscess.

Traditionally, there has been a standard practice for adolescent patients with PID to be hospitalized. This is not recommended and has not been found to improve outcomes unless any of the criteria for hospital-based care are present [224]. Despite antibiotic therapies, it is unclear if treatment can completely eradicate certain infections from the upper reproductive tract or if treatment can prevent long-term complications, such as ectopic pregnancy and tubal infertility. Another bacterium implicated in the pathogenesis of PID, and speculated to be a cause of endometriosis and tubal infertility, is *M. genitalium*. This is a relatively recently discovered mycoplasma (1983) and has been identified as a significant cause of urethritis [224]. The recommended treatment is azithromycin for at least five days.

Male Infertility

Endocrine disorders in men can be treated with exogenous gonadotropins directly or with oral antiestrogen medications (e.g., clomiphene) that stimulate the release of endogenous gonadotropins to boost testosterone levels. As with women, men with hyperprolactinemia may be prescribed bromocriptine. For obesity-related infertility, testosterone replacement therapy and aromatase inhibitors may be prescribed; maintenance and regulation of adipose-derived hormones (particularly leptin) should be a priority [84].

COMMON SURGICAL OR RADIOLOGIC INTERVENTIONS

There are many surgical interventions available to treat the causes of infertility. Many procedures that were traditionally performed "open" in the surgical department are now being performed laparoscopically using specialized instruments and imaging technologies.

Varicocele Repair

Microsurgical varicocelectomy is the treatment of choice for repairing varicocele and restoring normal blood flow and spermatogenesis due to the low risk of damage and high success rate compared with percutaneous varicocelectomy or laparoscopic repair [61]. The pregnancy rate after one year is 43% and after two years is 69%, compared with a rate of 16% in men with varicocele who elect to undergo insemination or hormone treatment. The procedure involves delivery of the testicle through an incision in the lower abdomen in order to accurately identify and preserve the testicular artery or arteries, cremasteric artery or arteries, lymphatic channels, and all internal spermatic veins and gubernacular veins. All defects may be repaired using this technique [61].

Laparoscopic Endometriosis Resection or Ablation

In cases of mild or moderate endometriosis, surgical treatment of adhesions or lesions has been shown to improve fertility and result in a small but significant increase in live birth rates [53]. One study found that ablation alone using a thermal coagulation device helped 10 out of 43 women with previous infertility to become pregnant, with no miscarriage or ectopic pregnancy reported [225]. Another study of fecundity outcomes of both resection and ablation concluded that about one-quarter of women with infertility would conceive within one year after surgical intervention [226]. However, another study using different measures found no improvement in pregnancy rates after either procedure compared with medication or no treatment [227]. In cases of mild-to-moderate endometriosis, the Practice Committee of the American Society for Reproductive Medicine states that there is insufficient evidence to recommend laparoscopy over expectant management [53].

In cases of severe endometriosis, conservative surgical interventions (including laparoscopy) have been found to significantly improve fertility and are recommended [53]. One study of 216 patients showed that pregnancy rates two years after laparoscopy or laparotomy were 45% and 63%, respectively [228]. Patients with ovarian endometriomas greater than 4 cm may benefit from laparoscopic cystectomy for improved fertility compared to cyst drainage and coagulation, which is associated with a high risk of cyst recurrence [229].

Fallopian Tube Microsurgical Reconstruction or Stenting

A 2010 retrospective study found that tubal microsurgery, including adhesiolysis, anastomosis, fimbrioplasty, salpingostomy, and refertilization after former sterilization, resulted in better pregnancy outcomes than one cycle of IVF treatment. Additionally, this approach results in fewer multiple births and related complications. Women can become pregnant many times after a single surgery versus having to potentially undergo multiple cycles of IVF treatments each time pregnancy is desired [230]. A 2006 Cochrane review found a significant increase in pregnancy rates attributable to microsurgery versus macrosurgery [231].

It should be noted that treating fallopian tube occlusion with manual pelvic physical therapy has been shown to restore patency in some women with confirmed bilateral occlusion [232]. A 2008 study used a 20-hour series of manual physical therapy treatments to improve soft tissue mobility and clear adhesions by indirectly manipulating the peritoneum, uterine/ovarian ligaments, and neighboring structures. Manual therapy restored unilateral or bilateral patency in 17 of the 28 patients, and 9 of those 17 patients reported a subsequent natural intrauterine pregnancy [232].

Laparoscopic Ovarian Drilling

Laparoscopic ovarian drilling procedures are a second-line treatment for women with PCOS when treatment with clomiphene/metformin or letrozole fails to induce ovulation. The procedure involves puncturing the ovary 5 to 10 times with an electrosurgical needle or laser fiber to reduce androgens. Patients with PCOS and high BMI (greater than 35), severe hyperandrogenism, and/or three or more years of infertility will generally respond positively to laparoscopic ovarian drilling. High LH levels are a good indicator of successful pregnancy after laparoscopic ovarian drilling [233]. Repetition of laparoscopic ovarian drilling treatments further improves PCOS symptoms, including infertility and hyperandrogenemia, in women sensitive to previous laparoscopic ovarian drilling [234]. Women who did not previously respond to medication treatments may be more responsive after laparoscopic ovarian drilling [234]. A multicenter observational study conducted between 2004 and 2013 examined the long-term pregnancy rate in 289 women with PCOS treated with ovarian drilling [235]. The average follow-up time was 28.4 months. One hundred thirty-seven (47.4%) women became pregnant following ovarian drilling; 71 (51.8%) of these pregnancies were spontaneous. Forty-eight (16.6%) women achieved at least two pregnancies following drilling, and 27 (56.3%) of these were spontaneous. Factors that predicted success were a normal BMI, an infertility period of less than three years, and an age younger than 35 years. Of the 33 women who underwent a second ovarian drilling, 19 (57.6%) achieved at least one pregnancy, and 10 (52.6%) of these were spontaneous [235].

ARTIFICIAL INSEMINATION

All types of artificial insemination procedures consist of using collected sperm to fertilize naturally occurring or medically stimulated oocytes. Although much attention is given to single and/or lesbian women as artificial insemination recipients, the treatment is largely used for heterosexual couples with male-factor infertility.

Intravaginal insemination (IVI) is typically used for healthy women wishing to become pregnant with donor semen, or less often, the semen of a partner with an ejaculatory problem (e.g., delayed or premature ejaculation). With IVI, a partner's or donor's semen is placed into a syringe and the semen is deposited near the cervix. IVI can take place at home or in an outpatient setting, and success rates are similar to natural conception rates.

Other forms of artificial insemination include [236]:

- Intracervical insemination (ICI): A syringe with flexible needle deposits semen inside the cervix.
- Intrauterine insemination (IUI): Semen is deposited into the uterus. A 2008 Cochrane review found that IUI has greater success than ICI.
- Intrafallopian insemination: Semen is placed directly in the fallopian tube. This technique is rarely used, expensive, and no more effective than IUI.

ASSISTED REPRODUCTIVE TECHNOLOGY

ART is an area of medical specialty serviced by reproductive endocrinologists. It can be useful for achieving pregnancy in women with tubal infertility or ovulatory infertility, particularly when pharmacologic fertility treatments and lifestyle modifications are not successful. Additionally, certain male factors necessitate the use of ART. Both donor eggs and donor sperm can be used for ART procedures.

In Vitro Fertilization

The first successful human conceived through IVF was born in 1978 in the United Kingdom. Her mother had been trying to conceive naturally for many years, and upon examination was found to have occluded fallopian tubes. This case is typical in that tubal infertility was once a distinct obstacle to pregnancy but has been greatly addressed by the development of IVF. Now more than 81,000 infants are born each year in the United States as a result of IVF [10].

The initial steps of IVF involve pharmacologic ovarian stimulation (to bring several oocytes to maturity simultaneously), oocyte retrieval, and sperm collection. Drugs typically given for ovarian stimulation include clomiphene, letrozole, FSH, LH, and hMG. Usually, these medications cause the ovaries to become very enlarged due to the development of an unusual number of follicles [237]. To help with oocyte maturation, human chorionic gonadotropin is administered, and GnRH agonists and antagonists are used to influence the timing of ovulation. The most common retrieval method involves an ultrasonically guided aspiration needle with a transvaginal approach. If a transvaginal method is not feasible, laparoscopic retrieval is used. During the brief procedure, several ovarian follicles are punctured to remove the mature oocytes. Studies indicate that the optimum number of oocytes to retrieve per cycle is 10 to 15 [238].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Society of Obstetricians and Gynaecologists of Canada recommends that all men with unexplained obstructive azoospermia be offered genetic/clinical counseling and genetic testing for cystic fibrosis prior to in vitro fertilization with ICSI.

(https://www.jogc.com/action/showPdf?pii=S1701-2163%2815%2930685-X. Last accessed June 12, 2020.)

Level of Evidence: II-2A (There is good evidence from well-designed cohort or case-control studies to recommend the clinical preventive action.)

Sperm is also collected, either through ejaculation or directly from the testicles (i.e., testicular sperm aspiration) or epididymis (i.e., microepididymal sperm aspiration) through needle aspiration. The sperm is then "washed" to remove seminal plasma and to form a concentrate. Sperm from men with HIV can also be washed to ensure the female partner will not be infected during conception.

The next stage of IVF is fertilization. Sperm and oocytes are incubated together in vitro or are combined by ICSI, whereby one sperm is injected directly into each oocyte; up to 70% of IVF cycles use ICSI [10]. Controversy has surrounded ICSI because the technician is responsible for choosing a healthy sperm and because somewhat higher rates of genetic defects are associated with the procedure due to overriding the natural competition/selection process. Hyaluronan binding assay (HBA) is now often used to assist sperm selection; however, so far studies have shown no significant benefit to fertilization/conception rates and the avoidance of congenital abnormalities with HBA prediction [239; 240]. Fertilization rates with incubation or ICSI are about 40% to 75% if the sperm and oocytes are of sufficient quality, but neither technique guarantees fertilization [237].

One to six days after retrieval, while at various stages of development, the embryos or blastocysts are suspended in a transfer medium. Drawn into the transfer catheter and inserted past the cervix, the embryo-containing medium is deposited into the uterus. The number of embryos transferred depends on age, health, and other factors decided by the reproductive endocrinologist and agreed upon by the client(s). For women younger than 35 years of age, it is recommended that only two embryos are transferred to prevent tripleting. Because blastocyst-stage embryos (days 5 to 7) are more likely to implant than cleavage-stage (day 2 or 3) embryos, fewer blastocysts should be transferred [241].

Intrafallopian Transfers

Zygote intrafallopian transfer (ZIFT) and gamete intrafallopian transfer (GIFT) are two spinoff treatments similar in some aspects to IVF. Though not technically IVF, GIFT shares the first steps of the process (i.e., ovarian stimulation, oocyte retrieval, and sperm collection). However, because ova and sperm are laparoscopically deposited into the fallopian tubes, fertilization does not take place in vitro. Immediately following retrieval, oocytes are mixed with collected and washed sperm and inserted, via the fimbrial end of the fallopian tube, into the ampulla. Advantages to GIFT are that the natural selection and competition of sperm still occurs and procedure times are greatly reduced compared with IVF. Certain semen parameters must be relatively normal (e.g., morphology, low DNA fragmentation), but others (e.g., motility, seminal fructose level) are less of a factor. Some couples may prefer using GIFT for religious reasons because fertilization takes place in vivo.

ZIFT treatments involve fertilization in vitro but use laparoscopy to deposit the zygote into the fallopian tube. ZIFT offers the advantage of confirmation of fertilization, and like GIFT, some patients who do not have success with IVF respond better to this type of treatment. GIFT and ZIFT combined represent less than 1% of ART treatment cycles performed in the United States today [10].

PSYCHOLOGICAL IMPACT OF INFERTILITY

Although infertility is a medical condition, it is also a relationship and social issue. As such, those coping with subfertility or infertility often also experience psychological consequences of the condition and its treatments. The psychological impact of infertility varies according to gender, degree of infertility, and other social and medical risk factors. Because these conditions so commonly co-present, it is vital that healthcare professionals involved in the care of patients with infertility consistently screen for and treat psychiatric conditions.

Mood disorders are relatively common in women and men with infertility, particularly before the initiation of treatment. However, women tend to display more distress than men in couples with infertility. In a study of 545 couples attending an infertility clinic, 30.8% of the women and 10.2% of the men presented a psychiatric diagnosis; of these, by far the most common were mood disorders, comprising 85% and 90% of all diagnoses, respectively [242]. The most common mood disorder was major depression. In another study, women being treated for infertility scored significantly lower on mental health subscales than the normative values [243]. A nationwide study conducted in Finland found that childless women with infertility were more likely to report depression and anxiety disorders (odds ratio: 3.4 and 2.7, respectively) than women who had not experienced infertility [244]. The researchers also found that women with infertility but with a current child had an increased risk for panic disorder (odds ratio: 2.6). Overall, it appears that the most common psychological effects of infertility on women are major depression and anxiety [242; 243; 244]. As discussed, principal concerns appear to center around the impact of infertility on relationships and the prospect of remaining childless [125].

Although much of the literature on psychological effects of infertility has focused on women, male partners in couples with infertility are also at risk for negative repercussions. A European study of 121 couples with infertility analyzed the psychological health of male partners [245]. The researchers found that depression, erectile dysfunction, and sexual problems were prevalent among male partners of couples with infertility. Furthermore, depression and anxiety, even at subthreshold levels, are associated with lower quality-of-life scores in men with infertility [246].

The relationship between infertility and psychiatric disorders is complex, and many factors can interact to increase the risk for developing depression and anxiety. Recognizing patients that may be at increased risk can lead to earlier diagnosis and treatment of psychological conditions. Duration of infertility is one such risk factor. Scores on depression

inventories are significantly higher among couples with infertility of one to three years' duration compared with those with infertility that has lasted one year or less [247]. Treatment failure is associated with increased levels of anxiety and depression during the treatment period and after the end of treatment [248]. On the other hand, women with infertility who do not seek medical advice have reported higher rates of depression and other mental health issues compared with women with infertility who do seek medical attention [249].

It has also been found that a diagnosis of infertility can precipitate depressive symptoms in women with certain personality types, coping styles, susceptibility to stress, and beliefs and values [250]. Researchers have identified women with lower levels of neuroticism and higher levels of extroversion and optimism to be at a lower risk for negative mental health consequences of an infertility diagnosis. Conversely, avoidance coping styles were associated with an increased risk for a more negative emotional response [250].

In one study, negative pregnancy test and obesity were independent risk factors for mood disorders in women undergoing IVF [251]. For their male partners, unexplained infertility was the only predictor. Unsuccessful IVF has also been shown to trigger grief responses and coping strategies in the couple with infertility [252]. Studies of patients starting IVF have found the strongest predictors of psychological distress to be passive and active coping, self-criticism, and dependency and intrusiveness [253].

ASSESSMENT

Due to the increased risk of psychiatric disorders in couples with infertility, a mental health assessment should be completed prior to initiating treatment of the infertility. This assessment should include a complete patient history, with specific attention paid to histories of mood disorders and stress [250; 254]. According to Wilkins and colleagues, some patients may be reluctant to disclose past psychiatric issues due to a fear of being refused infertility treatment [250]. Therefore, they recommend that healthcare professionals ask direct questions about mood and anxiety symptoms. Patients who display current evidence of psychiatric disorders should be referred for further treatment.

TREATMENT

Because psychiatric disorders are highly prevalent among individuals experiencing infertility, all healthcare professionals involved in their care, including gynecologists, endocrinologists, primary care clinicians, and mental health professionals, should be diligent in identifying and treating these disorders. Experts have recommended that psychotherapy, particularly supportive methods, should be considered as part of the general therapeutic framework of infertility treatment [255].

As with the general public, psychiatric disorders in men and women with infertility are generally treated with pharmacotherapy and/or psychotherapy. However, studies comparing the efficacy of different treatment modalities have been limited. Recommendations regarding treatment are made based on the patient's stage in infertility treatment (before, during, or after).

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the National Collaborating Centre for Women's and Children's Health, people who experience fertility problems should be offered counselling because fertility problems themselves, and the investigation and treatment of fertility problems, can cause psychologic stress.

(https://www.nice.org.uk/guidance/cg156. Last accessed June 16, 2023.)

Level of Evidence: Expert Opinion/Consensus Statement

Before initiating infertility treatments, patients who have depression should be treated based on general treatment guidelines. Patients who are experiencing high levels of stress should be instructed regarding stress reduction techniques, such as breathing exercises, imagery, and yoga [250]. Some experts recommend that men and women with stress levels higher than the established threshold practice intensive

stress reduction techniques for three months, after which they would be reassessed and restart infertility treatments [256]. The short-term goals of this intervention are to reduce feelings of helplessness, change sexual behaviors, modify negative cognitions, overcome knowledge deficiencies, and improve marital or partner communication skills [256].

Assessment of depressive symptoms and anxiety should continue during fertility treatment, and patients who display significant symptoms should be appropriately treated. It is important that the treatment with the least potential to harm the fetus, such as cognitive-behavioral therapy and interpersonal therapy, be attempted first. Some research has indicated that psychological interventions such as group therapy, psychotherapy, and cognitive-behavioral therapy during infertility treatment can lead to improvements in quality of life, mood/depressive symptoms, and treatment and pregnancy outcomes [257; 258]. One small study of 89 women with infertility and mild-to-moderate depression compared the use of cognitive-behavioral therapy, fluoxetine (20 mg daily), and a control group (no intervention) [259]. After 90 days, 79.3% of women in the cognitive-behavioral therapy group experienced improvements in depression symptoms. Comparatively, approximately 50% of the women in the fluoxetine group and 10% of the control group had significantly improved depression scores. However, women in the fluoxetine group did not show significant improvements in anxiety symptoms compared with the control group. The researchers concluded that "cognitive-behavioral therapy was not only a reliable alternative to pharmacotherapy but also was superior to fluoxetine in the resolution or reducing of depression and anxiety of infertile women" [259]. A randomized, controlled trial published in 2013 comparing cognitive-behavioral therapy to fluoxetine pharmacotherapy confirmed these results [125]. Support groups (both off- and online), art therapy, and psychoeducational interventions have also been found to be useful for patients with infertility [260; 261; 262].

If necessary, pharmacotherapy should be used during and after infertility treatment to treat patients with continued symptoms of depression or other mood disorders. In general, selective serotonin reuptake inhibitors are the first choice when treating depression and/or anxiety in women who are undergoing infertility treatment or who are pregnant [250]. There is conflicting evidence regarding the impact of various antidepressants in treatment failure and pregnancy rates in this patient population [250; 263]. As such, more research is necessary before a drug regimen can definitively be recommended for women being treated for subfertility or infertility.

IMPACT OF INFERTILITY ON MARITAL RELATIONSHIPS

Infertility will have a significant impact on the marital or partner relationship. There has been research indicating that the diagnosis can result in a marital benefit, defined as a strengthened and closer relationship [264]. It is important to enhance this effect, when possible. However, it is clear that a diagnosis of infertility and the subsequent stresses of treatment can also result in marital discord, partially due to differences in coping and emotional adjustment. In a study of 48 couples seeking fertility treatment, clear differences in husbands' and wives' approach to fertility treatment were evident [265]. The researchers found that women tended to be more invested and involved in the treatment process (e.g., more invested in having children, more interested in discussing the process, experience greater loss of self-esteem) than men. The greater the husband's involvement and interest in the treatment process and the better the quality of marital communication, the more likely that the diagnosis and experience would result in a marital benefit [265]. The authors of this study concluded that couples in infertility treatment may benefit from counseling or therapy to increase husbands' involvement and interest in fertility treatment and improve communication within the marriage.

CONCLUSION

Throughout history, infertility has had a tremendous stigma attached, and in many ways the attitudes toward and perceptions of individuals with infertility still exist today. It is important for all healthcare professionals to have a clear understanding of the many causes, risk factors, treatments, and psychological impacts of infertility in order to provide the best possible care to their patients. Promoting positive behaviors as part of preventive care and timely diagnosis, treatment, and referral to specialists will help to ensure that patients' quality of life is maintained and that stress during this difficult time is minimized.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. Gnoth C, Godehardt E, Frank-Herrmann P, Friol K, Tigges J, Freundl G. Definition and prevalence of subfertility and infertility. *Hum Reprod*. 2005;20(5):1144-1147.
2. MedlinePlus. Infertility. Available at https://medlineplus.gov/ency/article/001191.htm. Last accessed June 12, 2023.
3. Mayo Clinic. Infertility. Available at https://www.mayoclinic.org/diseases-conditions/infertility/symptoms-causes/syc-20354317. Last accessed June 12, 2023.
4. Centers for Disease Control and Prevention. Infertility and Impaired Fecundity in the United States 1982–2010. Data From the National Survey of Family Growth. Available at https://www.cdc.gov/nchs/data/nhsr/nhsr067.pdf. Last accessed June 12, 2023.
5. The American Congress of Obstetricians and Gynecologists. Treating Infertility. Available at https://www.acog.org/womens-health/faqs/treating-infertility. Last accessed June 12, 2023.
6. Paulsen CA, Berman NG, Wang C. Data from men in greater Seattle area reveals no downward trend in semen quality: further evidence that deterioration of semen quality is not geographically uniform. *Fertil Steril*. 1996;65(5):1015-1020.
7. Centers for Disease Control and Prevention. National Center for Health Statistics. National Survey of Family Growth: Key Statistics from the National Survey of Family Growth. Available at https://www.cdc.gov/nchs/nsfg/keystatistics.htm. Last accessed June 12, 2023.
8. Ferrara I, Balet R, Grudzinskas JG. Intrauterine donor insemination in single women and lesbian couples: a comparative study of pregnancy rates. *Hum Reprod*. 2000;15(3):621-625.
9. Cornell Institute for Reproductive Medicine. Understanding Male Infertility. Available at https://maleinfertility.org/understanding-male-infertility. Last accessed June 12, 2023.
10. Centers for Disease Control and Prevention. ART Success Rates. Available at https://www.cdc.gov/art/artdata/index.html. Last accessed June 12, 2023.
11. Mayo Clinic. Primary Ovarian Insufficiency. Available at https://www.mayoclinic.org/diseases-conditions/premature-ovarian-failure/symptoms-causes/syc-20354683. Last accessed June 12, 2023.
12. Cohen PG. The hypogonadal-obesity cycle: role of aromatase in modulating the testosterone-estradiol shunt—a major factor in the genesis of morbid obesity. *Med Hypotheses*. 1999;52(1):49-51.
13. Kyrou I, Tsigos C. Chronic stress, visceral obesity and gonadal dysfunction. *Hormones (Athens)*. 2008;7(4):287-293.
14. Medline Plus. Thyroid Diseases. Available at https://medlineplus.gov/thyroiddiseases.html. Last accessed June 12, 2023.
15. Andersson B, Mårin P, Lissner L, Vermeulen A, Björntorp P. Testosterone concentrations in women and men with NIDDM. *Diabetes Care*. 1994;17(5):405-411.
16. Park B, McPartland JM, Glass M. Cannabis, cannabinoids and reproduction. *Prostaglandins Leukot Essent Fatty Acids*. 2004;70(2):189-197.
17. Maccarrone M. Endocannabinoids: friends and foes of reproduction. *Prog Lipid Res*. 2009;48(6):344-354.
18. Taylor AH, Amoako AA, Bambang K, et al. Endocannabinoids and pregnancy. *Clin Chim Acta*. 2010;411(13-14):921-930.
19. Das SK, Paria BC, Chakraborty I, Dey SK. Cannabinoid ligand-receptor signaling in the mouse uterus. *Proc Natl Acad Sci USA*. 1995;92(10):4332-4336.
20. Wang H, Dey SK, Maccarrone M. Jekyll and Hyde: two faces of cannabinoid signaling in male and female fertility. *Endocr Rev*. 2006;27(5):427-448.
21. McPartland JM. The endocannabinoid system: an osteopathic perspective. *J Am Osteopath Assoc*. 2008;108(10):586-600.
22. Visser JA, de Jong FH, Laven JS, Themmen AP. Anti-Müllerian hormone: a new marker for ovarian function. *Reproduction*. 2006;131(1):1-9.
23. American Pregnancy Association. Premature Ovarian Failure: Premature Menopause. Available at https://americanpregnancy.org/womens-health/premature-ovarian-failure/. Last accessed June 12, 2023.
24. Kevenaar ME, Meerasahib MF, Kramer P, et al. Serum anti-mullerian hormone levels reflect the size of the primordial follicle pool in mice. *Endocrinology*. 2006;147(7):3228-3234.
25. Pansini F, Bergamini CM, Cavallini AR, et al. Prolactinemia during the menstrual cycle: a possible role for prolactin in the regulation of ovarian function. *Gynecol Obstet Invest*. 1987;23(3):172-176.
26. Paduch DA, Bolyakov A, Cohen P, Travis A. Reproduction in men with Klinefelter syndrome: the past, the present, and the future. *Semin Reprod Med*. 2009;27(2):137-148.
27. Roberts A. *The Complete Human Body*. 2nd ed. New York, NY: DK Publishing; 2016.
28. Heller CG, Clermont Y. Spermatogenesis in man: an estimate of its duration. *Science*. 1963;140:184-186.
29. Loverro G, Nappi L, Vicino M, Carriero C, Vimercati A, Selvaggi L. Uterine cavity assessment in infertile women: comparison of transvaginal sonography and hysteroscopy. *Eur J Obstet Gynecol Reprod Biol*. 2001;100(1):67-71.

30. The Merck Manuals. Abnormal Cervical Mucus. Available at http://www.merckmanuals.com/professional/gynecology-and-obstetrics/infertility/abnormal-cervical-mucus. Last accessed June 12, 2023.
31. Southern California Center for Reproductive Medicine. Exploring the Relationship Between Age and Fertility. Available at https://www.socalfertility.com/fertility-treatment/age-fertility. Last accessed June 12, 2023.
32. Yu SL, Yap C. Investigating the infertile couple. *Ann Acad Med Singapore*. 2003;32(5):611-613.
33. Terzioglu F. Investigation into effectiveness of counseling on assisted reproductive techniques in Turkey. *J Psychosom Obstet Gynaecol*. 2001;22(3):133-141.
34. Creatsas G, Deligeoroglou E. Vaginal aplasia and reconstruction. *Best Pract Res Clin Obstet Gynaecol*. 2010;24(2):185-191.
35. The Merck Manuals Online Library. Amenorrhea. Available at http://www.merckmanuals.com/professional/gynecology-and-obstetrics/menstrual-abnormalities/amenorrhea?qt=&sc=&alt=. Last accessed June 12, 2023.
36. Strauss JE, Barbieri RL (eds).*Yen and Jaffe's Reproductive Endocrinology*. 7th ed. Saunders Elsevier: Philadelphia, PA; 2014.
37. U.S. Department of Health and Human Services. Polycystic Ovary Syndrome. Available at https://www.womenshealth.gov/a-z-topics/polycystic-ovary-syndrome. Last accessed June 12, 2023.
38. Mayo Clinic. Polycystic Ovary Syndrome. Available at https://www.mayoclinic.org/diseases-conditions/pcos/symptoms-causes/syc-20353439. Last accessed June 12, 2023.
39. Penn State Milton S. Hershey Medical Center. Polycystic Ovary Syndrome. Available at http://pennstatehershey.adam.com/content.aspx?productId=117&pid=1&gid=000369. Last accessed May 4, 2020.
40. Katsiki N, Hatzitolios AI. Insulin-sensitizing agents in the treatment of polycystic ovary syndrome: an update. *Curr Opin Obstet Gynecol*. 2010;22(6):466-476.
41. Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. *Reproduction*. 2010;140(3):399-410.
42. Sotrel G. Is surgical repair of the fallopian tubes ever appropriate? *Rev Obstet Gynecol*. 2009;2(3):176-185.
43. Malhotra N, Kumar P, Malhotra J, Bora NM, Mittal P (eds). *Jeffcoate's Principles of Gynaecology*. 8th ed. New Delhi, India: Jaypee Brothers; 2014.
44. Mohiyiddeen L, Hardiman A, Fitzgerald C, et al. Tubal flushing for subfertility. *Cochrane Database Syst Rev*. 2015;(5):CD003718.
45. National Collaborating Centre for Women's and Children's Health. *Fertility: Assessment and Treatment for People with Fertility Problems*. London: RCOG Press; 2014.
46. MedlinePlus. Pelvic Inflammatory Disease (PID). Available at https://medlineplus.gov/ency/article/000888.htm. Last accessed June 12, 2023.
47. Igra V. Pelvic inflammatory disease in adolescents. *AIDS Patient Care STDS*. 1998;12(2):109-124.
48. Haggerty CL, Gottlieb SL, Taylor BD, Low N, Xu F, Ness RB. Risk of sequelae after Chlamydia trachomatis genital infection in women. *J Infect Dis*. 2010;201(Suppl 2):134-155.
49. Quan M. Pelvic inflammatory disease: diagnosis and management. *J Am Board Fam Pract*. 1994;7(2):110-123.
50. Washington AE, Sweet RL, Shafer MA. Pelvic inflammatory disease and its sequelae in adolescents. *J Adolesc Health Care*. 1985;6(4):298-310.
51. Baird DD, Weinberg CR, Voigt LF, Daling JR. Vaginal douching and reduced fertility. *Am J Public Health*. 1996;86(6):844-850.
52. Witz CA, Burns WN. Endometriosis and infertility: is there a cause and effect relationship? *Gynecol Obstet Invest*. 2002;53(Suppl 1):2-11.
53. Practice Committee of the American Society for Reproductive Medicine. Endometriosis and infertility: a committee opinion. *Fertil Steril*. 2012;98(3):591-598.
54. Mueller BA, Daling JR, Moore DE, et al. Appendectomy and the risk of tubal infertility. *N Engl J Med*. 1986;315(24):1506-1508.
55. Arai T, Kitahara S, Horiuchi S, Sumi S, Yoshida K. Relationship of testicular volume to semen profiles and serum hormone concentrations in infertile Japanese males. *Int J Fertil Womens Med*. 1998;43(1):40-47.
56. Shafi H, Esmaeilzadeh S, Delavar MA, Haydari FH, Mahdinejad N, Abedi S. Prevalence of varicocele among primary and secondary infertile men: association with occupation, smoking, and drinking alcohol. *N Am J Med Sci*. 2014;6(10):532-535.
57. Thomas JC, Elder JS. Testicular growth arrest and adolescent varicocele: does varicocele size make a difference? *J Urol*. 2002;168 (4 Pt 2):1689-1691.
58. Kass EJ, Stork BR, Steinert BW. Varicocele in adolescence induces left and right testicular volume loss. *BJU Int*. 2001;87(6):499-501.
59. Chan PT, Goldstein M. Medical backgrounder on varicocele. *Drugs Today (Barc)*.2002;38(1):59-67.
60. American Society for Reproductive Medicine. Report on Varicocele and Infertility: a Committee Opinion. Available at https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/report_on_varicocele.pdf. Last accessed June 12, 2023.
61. Mayo Clinic. Varicocele. Available at https://www.mayoclinic.org/diseases-conditions/varicocele/symptoms-causes/syc-20378771. Last accessed June 12, 2023.

62. World Health Organization. The influence of varicocele on parameters of fertility in a large group of men presenting to infertility clinics. *Fertil Steril.* 1992;57(6):1289.
63. de Kretser DM. Editorial: Is spermatogenic damage associated with Leydig cell dysfunction? *J Clin Endocrinol Metab.* 2004;89(7):3158-3160.
64. Joensen UN, Jørgensen N, Rajpert-De Meyts E, Skakkebæk NE. Testicular dysgenesis syndrome and Leydig cell function. *Basic Clin Pharmacol Toxicol.* 2008;102(2):155-161.
65. Andersson AM, Jørgensen N, Frydelund-Larsen L, Rajpert-De Meyts E, Skakkebaek NE. Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile controls. *J Clin Endocrinol Metab.* 2004;89(7):3161-3167.
66. Ramphul K, Zulfiqar H, Mejias SG. Sertoli-Cell-Only-Syndrome. Treasure Island, FL: StatPearls Publishing; 2020.
67. Tzvetkova P. Congenital anomalies of the mesonephric duct and fertility. *Acta Chir Iugosl.* 2007;54(2):63-67.
68. Biswas S, Ferguson KM, Stedronska J, Baffoe G, Mansfield MD, Kosbab MH. Fructose and hormone levels in semen: their correlations with sperm counts and motility. *Fertil Steril.* 1978;30(2):200-204.
69. Schirren C. Relation between fructose content of semen and fertility in man. *J Reprod Fertil.* 1963;5:347-358.
70. Tremellen K. Oxidative stress and male infertility-a clinical perspective. *Hum Reprod Update.* 2008;14(3):243-258.
71. Ruder EH, Hartman TJ, Goldman MB. Impact of oxidative stress on female fertility. *Curr Opin Obstet Gynecol.* 2009;21(3):219-222.
72. Shefi S, Tarapore PE, Walsh TJ, Croughan M, Turek PJ. Wet heat exposure: a potentially reversible cause of low semen quality in infertile men. *Int Braz J Urol.* 2007;33(1):50-56.
73. Kumar S, Kumari A, Murarka S. Lifestyle factors in deteriorating male reproductive health. *Indian J Exp Biol.* 2009;47(8):615-624.
74. Hudson MM. Late complications after leukemia therapy. In: Pui CH (ed). *Childhood Leukemias.* 2nd ed. New York, NY: Cambridge University Press; 2006: 750-773.
75. Dickerman JD. The late effects of childhood cancer therapy. *Pediatrics.* 2007;119(3):554-568.
76. Children's Oncology Group. Long-term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Available at http://www.survivorshipguidelines.org/pdf/LTFUGuidelines.pdf. Last accessed June 12, 2023.
77. Friedman D, Meadows AT. Late effects following lymphoma treatment. In: Weinstein HJ, Hudson MH, Link MP (eds). *Pediatric Lymphomas.* Berlin: Springer; 2007: 259-280.
78. Heath JA. Monitoring after childhood cancer-an update for GPs. *Aust Fam Physician.* 2005;34(9):761-767.
79. Geenen MM, Cardous-Ubbink MC, Kremer LC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA.* 2007;297(24):2705-2715.
80. Horning S, Hoppe RT, Kaplan HS, Rosenberg SA. Female reproductive potential after treatment for Hodgkin's disease. *N Engl J Med.* 1981;304(23):1377-1382.
81. Oeffinger KC, Mertens AC, Hudson MM, et al. Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Ann Fam Med.* 2004;2(1):61-70.
82. Centers for Disease Control and Prevention. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017–2018. Available at https://www.cdc.gov/nchs/products/databriefs/db360.htm. last accessed June 12, 2023.
83. Clark AM, Ledger W, Galletly C, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. *Hum Reprod.* 1995;10(10):2705-2712.
84. Cabler S, Agarwal A, Flint M, du Plessis SS. Obesity: modern man's fertility nemesis. *Asian J Androl.* 2010;12(4):480-489.
85. Du Plessis SS, Cabler S, McAlister DA, Sabanegh E, Agarwal A. The effect of obesity on sperm disorders and male infertility. *Nat Rev Urol.* 2010;7(3):153-161.
86. Brewer CJ, Balen AH. The adverse effects of obesity on conception and implantation. *Reproduction.* 2010;140(3):347-364.
87. Norman JE. The adverse effects of obesity on reproduction. *Reproduction.* 2010;140(3):343-345.
88. Pandey S, Bhattacharya S. Impact of obesity on gynecology. *Womens Health (Lond Engl).* 2010;6(1):107-117.
89. Kuchenbecker WK, Groen H, Zijlstra TM, et al. The subcutaneous abdominal fat and not the intraabdominal fat compartment is associated with anovulation in women with obesity and infertility. *J Clin Endocrinol Metab.* 2010;95(5):2107-2112.
90. Wilkes S, Murdoch A. Obesity and female fertility: a primary care perspective. *J Fam Plann Reprod Health Care.* 2009;35(3):181-185.
91. van der Steeg JW, Steures P, Eijkemans MJ, et al. Obesity affects spontaneous pregnancy chances in subfertile, ovulatory women. *Hum Reprod.* 2008;23(2):324-328.
92. Nawaz FH, Rizvi J. Continuation of metformin reduces early pregnancy loss in obese Pakistani women with polycystic ovarian syndrome. *Gynecol Obstet Invest.* 2010;69(3):184-189.
93. Chavarro JE, Toth TL, Wright DL, Meeker JD, Hauser R. Body mass index in relation to semen quality, sperm DNA integrity, and serum reproductive hormone levels among men attending an infertility clinic. *Fertil Steril.* 2010;93(7):2222-2231.
94. Hammoud AO, Gibson M, Peterson CM, Meikle AW, Carrell DT. Impact of male obesity on infertility: a critical review of the current literature. *Fertil Steril.* 2008;90(4):897-904.

95. Simon D, Charles MA, Nahoul K, et al. Association between plasma total testosterone and cardiovascular risk factors in healthy adult men: the Telecom Study. *J Clin Endocrinol Metab*. 1997;82(2):682-685.
96. Ghanayem BI, Bai R, Kissling GE, Travlos G, Hoffler U. Diet-induced obesity in male mice is associated with reduced fertility and potentiation of acrylamide-induced reproductive toxicity. *Biol Reprod*. 2010;82(1):96-104.
97. Miller WL, Strauss JF 3rd. Molecular pathology and mechanism of action of the steroidogenic acute regulatory protein, StAR. *J Steroid Biochem Mol Biol*. 1999;69(1-6):131-141.
98. Jonasson JM, Brismar K, Sparén P, et al. Fertility in women with type 1 diabetes: a population-based cohort study in Sweden. *Diabetes Care*. 2007;30(9):2271-2276.
99. Greenbaum CJ. Insulin resistance in type 1 diabetes. *Diabetes Metab Res Rev*. 2002;18(3):192-200.
100. Livshits A, Seidman DS. Fertility issues in women with diabetes. *Womens Health (Lond Engl)*. 2009;5(6):701-707.
101. Chia YT, Chua S, Thai AC, Kek LP, Ratnam SS. Congenital abnormalities and pregestational diabetes mellitus in pregnancy. *Singapore Med J*. 1996;37(4):380-383.
102. Bánhidy F, Acs N, Puhó EH, Czeizel AE. Congenital abnormalities in the offspring of pregnant women with type 1, type 2 and gestational diabetes mellitus: a population-based case-control study. *Congenit Anom (Kyoto)*. 2010;50(2):115-121.
103. La Vignera S, Lanzafame F, Di Mauro M, Condorelli R, Vicari E. Spermatic and ultrasound characterization of young diabetic patients. *Arch Ital Urol Androl*. 2009;81(4):245-247.
104. Mircea CN, Lujan ME, Pierson RA. Metabolic fuel and clinical implications for female reproduction. *J Obstet Gynaecol Can*. 2007;29(11):887-902.
105. Hurvitz M, Weiss R. The young female athlete. *Pediatr Endocrinol Rev*. 2009;7(2):123-129.
106. Welt CK, Chan JL, Bullen J, et al. Recombinant human leptin in women with hypothalamic amenorrhea. *N Engl J Med*. 2004;351(10):987-997.
107. Micali N, Simonoff E, Treasure J. Risk of major adverse perinatal outcomes in women with eating disorders. *Br J Psychiatry*. 2007;190:255-259.
108. Turner TT, Lysiak JJ. Oxidative stress: a common factor in testicular dysfunction. *J Androl*. 2008;29(5);488-498.
109. Agarwal A, Hamada A, Esteves SC. Insight into oxidative stress in varicocele-associated male infertility: part 1. *Nat Rev Urol*. 2012;9(12):678-690.
110. Andersen AE, Ryan GL. Eating disorders in the obstetric and gynecologic patient population. *Obstet Gynecol*. 2009;114(6):1353-1367.
111. Savitz DA, Stein CR, Siega-Riz AM, Herring AH. Gestational weight gain and birth outcome in relation to prepregnancy body mass index and ethnicity. *Ann Epidemiol*. 2011;21(2):78-85.
112. Homan GF, Davies M, Norman R. The impact of lifestyle factors on reproductive performance in the general population and those undergoing infertility treatment: a review. *Hum Reprod Update*. 2007;13(3):209-223.
113. Fontana R, Della Torre S. The deep correlation between energy metabolism and reproduction: a view on the effects of nutrition for women fertility. *Nutrients*. 2016;8(2):87.
114. Cederroth CR, Auger J, Zimmermann C, Eustache F, Nef S. Soy, phyto-oestrogens and male reproductive function: a review. *Int J Androl*. 2010;33(2):304-316.
115. Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC. A prospective study of dairy foods intake and anovulatory infertility. *Hum Reprod*. 2007;22(5):1340-1347.
116. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Protein intake and ovulatory infertility. *Am J Obstet Gynecol*. 2008;198(2):210.e1-7.
117. Räikkönen K, Keltikangas-Järvinen L, Adlercreutz H, Hautanen A. Psychosocial stress and the insulin resistance syndrome. *Metabolism*. 1996;45(12):1533-1538.
118. Chandola T, Brunner E, Marmot M. Chronic stress at work and the metabolic syndrome: prospective study. *BMJ*. 2006;332(7540):521-525.
119. Pizent A, Jurasović J, PavlovićM, Telisman S. Serum copper, zinc and selenium levels with regard to psychological stress in men. *J Trace Elem Med Biol*. 1999;13(1-2):34-39.
120. Muneyyirci-Delale O, Goldstein D, Reyes FI. Diagnosis of stress-related hyperprolactinemia: evaluation of the hyperprolactinemia rest test. *N Y State J Med*. 1989;89(4):205-208.
121. Buck Louis GM, Lum KJ, Sundaram R, et al. Stress reduces conception probabilities across the fertile window: evidence in support of relaxation. *Fertil Steril*. 2011;95(7):2184-2189.
122. Gallinelli A, Roncaglia R, Matteo ML, Ciaccio I, Volpe A, Facchinetti F. Immunological changes and stress are associated with different implantation rates in patients undergoing in vitro fertilization-embryo transfer. *Fertil Steril*. 2001;76(1):85-91.
123. Domar AD, Clapp D, Slawsby E, Kessel B, Orav J, Freizinger M. The impact of group psychological interventions on distress in infertile women. *Health Psychol*. 2000;19(6):568-575.

124. Domar AD, Clapp D, Slawsby EA, Dusek J, Kessel B, Freizinger M. Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil Steril.* 2000;73(4):805-811.

125. Faramarzi M, Pasha H, Esmailzadeh S, Kheirkhah F, Heidary S, Afshar Z. The effect of the cognitive behavioral therapy and pharmacotherapy on infertility stress: a randomized controlled trial. *Int J Fertil Steril.* 2013;7(3):199-206.

126. Centers for Disease Control and Prevention. STDs and Infertility. Available at https://www.cdc.gov/std/infertility/default.htm. Last accessed June 12, 2023.

127. Eggert-Kruse W, Buhlinger-Gopfarth N, Rohr G, et al. Antibodies to Chlamydia trachomatisin semen and relationship with parameters of male fertility. *Hum Reprod.* 1996;11(7):1408-1417.

128. Grodstein F, Goldman MB, Cramer DW. Relation of tubal infertility to history of sexually transmitted diseases. *Am J Epidemiol.* 1993;137(5):577-584.

129. ESHRE Task Force on Ethics and Law, Dondorp W, de Wert G, Pennings G, et al. Lifestyle-related factors and access to medically assisted reproduction. *Hum Reprod.* 2010;25(3):578-583.

130. Grodstein F, Goldman MB, Cramer DW. Infertility in women and moderate alcohol use. *Am J Public Health.* 1994;84(9):1429-1432.

131. Jensen TK, Hjollund NH, Henriksen TB, et al. Does moderate alcohol consumption affect fertility? Follow up study among couples planning first pregnancy. *BMJ.* 1998;317(7157):505-510.

132. Eggert J, Theobald H, Engfeldt P. Effects of alcohol consumption on female fertility during an 18-year period. *Fertil Steril.* 2004;81(2):379-383.

133. Joesoef MR, Beral V, Aral SO, Rolfs RT, Cramer DW. Fertility and use of cigarettes, alcohol, marijuana, and cocaine. *Ann Epidemiol.* 1993;3(6):592-594.

134. Dunphy BC, Barratt CL, Cooke ID. Male alcohol consumption and fecundity in couples attending an infertility clinic. *Andrologia.* 1991;23(3):219-221.

135. Marinelli D, Gaspari L, Pedotti P, Taioli E. Mini-review of studies on the effect of smoking and drinking habits on semen parameters. *Int J Hyg Environ Health.* 2004;207(3):185-192.

136. Pajarinen J, Karhunen PJ, Savolainen V, Lalu K, Penttilä A, Laippala P. Moderate alcohol consumption and disorders of human spermatogenesis. *Alcohol Clin Exp Res.* 1996;20(2):332-337.

137. Kalyani R, Basavaraj PB, Kumar ML. Factors influencing quality of semen: a two-year prospective study. *Indian J Pathol Microbiol.* 2007;50(4):890-895.

138. Gaur DS, Talekar MS, Pathak VP. Alcohol intake and cigarette smoking: impact of two major lifestyle factors on male fertility. *Indian J Pathol Microbiol.* 2010;53(1):35-40.

139. U.S. Department of Health and Human Services. Reports and Detailed Tables from the 2015 National Survey on Drug Use and Health: National Findings. Available at https://www.samhsa.gov/data/report/2019-nsduh-detailed-tables. Last accessed June 12, 2023.

140. Mitchell DC, Knight CA, Hockenberry J, Teplansky R, Hartman TJ. Beverage caffeine intakes in the U.S. *Food Chemical Toxicol.* 2014;63:136-142.

141. Arabi M. Nicotinic infertility: assessing DNA and plasma membrane integrity of human spermatozoa. *Andrologia.* 2004;36(5):305-310.

142. Augood C, Duckitt K, Templeton AA. Smoking and female infertility: a systematic review and meta-analysis. *Hum Reprod.* 1998;13(6):1532-1539.

143. Vrsanská S, Nagyová E, Mlynarcíková A, Ficková M, Kolena J. Components of cigarette smoke inhibit expansion of oocyte-cumulus complexes from porcine follicles. *Physiol Res.* 2003;52(3):383-387.

144. Collodel G, Capitani S, Iacoponi F, Federico MG, Pascarelli NA, Moretti E. Retrospective assessment of potential negative synergistic effects of varicocele and tobacco use on ultrastructural sperm morphology. *Urology.* 2009;74(4):794-799.

145. Bordel R, Laschke MW, Menger MD, Vollmar B. Nicotine does not affect vascularization but inhibits growth of freely transplanted ovarian follicles by inducing granulosa cell apoptosis. *Hum Reprod.* 2006;21(3):610-617.

146. Fraga CG, Motchnik PA, Wyrobek AJ, Rempel DM, Ames BN. Smoking and low antioxidant levels increase oxidative damage to sperm DNA. *Mutat Res.* 1996;351(2):199-203.

147. Moustafa MH, Sharma RK, Thornton J, et al. Relationship between ROS production, apoptosis and DNA denaturation in spermatozoa from patients examined for infertility. *Hum Reprod.* 2004;19(1):129-138.

148. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. *Int J Environ Res Public Health.* 2009;6(2):445-462.

149. Waylen AL, Metwally M, Jones GL, Wilkinson AJ, Ledger WL. Effects of cigarette smoking upon clinical outcomes of assisted reproduction: a meta-analysis. *Hum Reprod Update.* 2009;15(1):31-44.

150. Tsadilas CD. Soil pH influence on cadmium uptake by tobacco in high cadmium exposure. *J Plant Nutr.* 2000;23(8):1167-1178.

151. Dechanet C, Anahory T, Mathieu Daude JC, et al. Effects of cigarette smoking on reproduction. *Hum Reprod Update.* 2011;17(1):76-95.

152. Omu AE, Dashti H, Mohamed AT, Mattappallil AB. Significance of trace elements in seminal plasma of infertile men. *Nutrition*. 1995;11(5 Suppl):502-505.

153. Mlynarcikova A, Fickova M, Scsukova S. Ovarian intrafollicular processes as a target for cigarette smoke components and selected environmental reproductive disruptors. *Endocr Regul*. 2005;39(1):21-32.

154. Mayo Clinic. Caffeine Content for Coffee, Tea, Soda, and More. Available at http://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/art-20049372. Last accessed June 12, 2023.

155. Bolúmar F, Olsen J, Rebagliato M, Bisanti L. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. European Study Group on Infertility Subfecundity. *Am J Epidemiol*. 1997;145(4):324-334.

156. Jensen TK, Henriksen TB, Hjollund NH, et al. Caffeine intake and fecundability: a follow-up study among 430 Danish couples planning their first pregnancy. *Reprod Toxicol*. 1998;12(3):289-295.

157. Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. *Am J Epidemiol*. 1997;146(1):32-41.

158. Nagata C, Kabuto M, Shimizu H. Association of coffee, green tea, and caffeine intakes with serum concentrations of estradiol and sex hormone-binding globulin in premenopausal Japanese women. *Nutr Cancer*. 1998;30(1):21-24.

159. Lucero J, Harlow BL, Barbieri RL, Sluss P, Cramer DW. Early follicular phase hormone levels in relation to patterns of alcohol, tobacco, and coffee use. *Fertil Steril*. 2001;76(4):723-729.

160. Chavarro JE, Rich-Edwards JW, Rosner BA, Willett WC. Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility. *Epidemiology*. 2009;20(3):374-381.

161. Fenster L, Quale C, Waller K, et al. Caffeine consumption and menstrual function. *Am J Epidemiol*. 1999;149(6):550-557.

162. Joesoef MR, Beral V, Rolfs RT, Aral SO, Cramer DW. Are caffeinated beverages risk factors for delayed conception? *Lancet*. 1990;335(8682):136-137.

163. Hakim RB, Gray RH, Zacur H. Alcohol and caffeine consumption and decreased fertility. *Fertil Steril*. 1998;70(4):632-637.

164. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. *Lancet*. 1988;2(8626-8627):1453-1456.

165. Caan B, Quesenberry CP Jr, Coates AO. Differences in fertility associated with caffeinated beverage consumption. *Am J Public Health*. 1998;88(2):270-274.

166. American Pregnancy Association. Caffeine During Pregnancy. Available at https://americanpregnancy.org/pregnancy-health/caffeine-intake-during-pregnancy/. Last accessed June 12, 2023.

167. National Institute on Drug Abuse. NIDA Infofacts: Marijuana. Available at https://www.drugabuse.gov/publications/drugfacts/marijuana. Last accessed June 12, 2023.

168. Amoako AA, Marczylo TH, Marczylo EL, et al. Anandamide modulates human sperm motility: implications for men with asthenozoospermia and oligoasthenoteratozoospermia. *Hum Reprod*. 2013;28(8):2058-2066.

169. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol*. 2008;21(2):494-502.

170. Daling JR, Doody DR, Sun X, et al. Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer*. 2009;115(6):1215-1223.

171. Mueller BA, Daling JR, Weiss NS, Moore DE. Recreational drug use and the risk of primary infertility. *Epidemiology*. 1990;1(3): 195-200.

172. Badawy ZS, Chohan KR, Whyte DA, Penefsky HS, Brown OM, Souid AK. Cannabinoids inhibit the respiration of human sperm. *Fertil Steril*. 2009;91(6):2471-2476.

173. Whan LB, West MC, McClure N, Lewis SE. Effects of delta-9-tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana, on human sperm function in vitro. *Fertil Steril*. 2006;85(3):653-660.

174. Jukic AM, Weinberg CR, Baird DD, Wilcox AJ. Lifestyle and reproductive factors associated with follicular phase length. *J Womens Health (Larchmt)*. 2007;16(9):1340-1347.

175. Nassan FL, Arvizu M, Mínguez-Alarcón L, et al. Marijuana smoking and markers of testicular function among men from a fertility centre. *Hum Reprod*. 2019;34(4):715-723.

176. Talevi R, Barbato V, De Iorio S, et al. Is there a role for endocannabinoids in sperm-oviduct interaction? *Reproduction*. 2010;140(2):247-257.

177. Sanders L. Pore propulsion helps out sperm: study suggests possible link between marijuana, infertility. *Sci News*. 2010;177(5):12.

178. Bracken MB, Eskenazi B, Sachse K, McSharry JE, Hellenbrand K, Leo-Summers L. Association of cocaine use with sperm concentration, motility, and morphology. *Fertil Steril*. 1990;53(2):315-322.

179. Ragni G, De Lauretis L, Gambaro V, et al. Semen evaluation in heroin and methadone addicts. *Acta Eur Fertil*. 1985;16(4):245-249.

180. Wang C, Chan V, Yeung RT. The effect of heroin addiction on pituitary-testicular function. *Clin Endocrinol (Oxf)*. 1978;9(5):455-461.

181. Xiao D, Liu M, Zhang Y, et al. Research on sex hormone changes in female heroin reliers. *Chinese J Lab Diagn*. 2004;8(3):281-282.

182. Facchinetti F, Volpe A, Farci G, et al. Hypothalamus-pituitary-adrenal axis of heroin addicts. *Drug Alcohol Depend*. 1985;15(4):361-366.
183. Wells PG, McCallum GP, Lam KC, Henderson JT, Ondovcik SL. Oxidative DNA damage and repair in teratogenesis and neurodevelopmental deficits. *Birth Defects Res C Embryo Today*. 2010;90(2):103-109.
184. Yamamoto Y, Yamamoto K, Hayase T. Effect of methamphetamine on male mice fertility. *J Obstet Gynaecol Res*. 1999;25(5):353-358.
185. Yamamoto Y, Yamamoto K, Hayase T, Abiru H, Shiota K, Mori C. Methamphetamine induces apoptosis in seminiferous tubules in male mice testis. *Toxicol Appl Pharmacol*. 2002;178(3):155-160.
186. Gazvani MR, Buckett W, Luckas MJ, Aird IA, Hipkin LJ, Lewis-Jones DI. Conservative management of azoospermia following steroid abuse. *Hum Reprod*. 1997;12(8):1706-1708.
187. Poch MA, Sigman M. Clinical evaluation and treatment of male factor infertility. In: Carroll DT, Peterson CM (ed). *Reproductive Endocrinology and Infertility: Integrating Modern Clinical and Laboratory Practice*. New York, NY: Springer; 2010: 367-378.
188. Rosen RC, Kostis JB, Jekelis AW. Beta-blocker effects on sexual function in normal males. *Arch Sex Behav*. 1988;17(3):241-255.
189. Giuliano F, Bernabe J, Droupy S, Alexandre L, Allard J. A comparison of the effects of tamsulosin and alfuzosin on neurally evoked increases in bladder neck and seminal vesicle pressure in rats. *BJU Int*. 2004;93(4):605-608.
190. Giuliano FA, Clément P, Denys P, Alexandre L, Bernabé J. Comparison between tamsulosin and alfuzosin on the expulsion phase of ejaculation in rats. *BJU Int*. 2006;98(4):876-879.
191. Hellstrom WJ, Sikka SC. Effects of acute treatment with tamsulosin versus alfuzosin on ejaculatory function in normal volunteers. *J Urol*. 2006;176(4 Pt 1):1529-1533.
192. Baranski B. Effects of the workplace on fertility and related reproductive outcomes. *Environ Health Perspect*. 1993;101(Suppl 2): 81-90.
193. Bonde JP. The risk of male subfecundity attributable to welding of metals. Studies of semen quality, infertility, fertility, adverse pregnancy outcome and childhood malignancy. *Int J Androl*. 1993;16(Suppl 1):1-29.
194. Eskenazi B, Fenster L, Hudes M, et al. A study of the effect of perchloroethylene exposure on the reproductive outcomes of wives of dry-cleaning workers. *Am J Ind Med*. 1991;20(5):593-600.
195. Doyle P, Roman E, Beral V, Brookes M. Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. *Occup Environ Med*. 1997;54(12):848-853.
196. Fei C, McLaughlin JK, Lipworth L, Olsen J. Maternal levels of perfluorinated chemicals and subfecundity. *Hum Reprod*. 2009;24(5):1200-1205.
197. Swan SH. Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans. *Environ Res*. 2008;108(2):177-184.
198. Chatterjee S, Karlovsky P. Removal of the endocrine disrupter butyl benzyl phthalate from the environment. *Appl Microbiol Biotechnol*. 2010;87(1):61-73.
199. Lyche JL, Gutleb AC, Bergman A, et al. Reproductive and developmental toxicity of phthalates. *J Toxicol Environ Health B Crit Rev*. 2009;12(4):225-249.
200. Witorsch RJ, Thomas JA. Personal care products and endocrine disruption: a critical review of the literature. *Crit Rev Toxicol*. 2010;40(Suppl 3):1-30.
201. Meeker JD, Calafat AM, Hauser R. Urinary bisphenol A concentrations in relation to serum thyroid and reproductive hormone levels in men from an infertility clinic. *Environ Sci Technol*. 2010;44(4):1458-1463.
202. Mok-Lin E, Ehrlich S, Williams PL, et al. Urinary bisphenol A concentrations and ovarian response among women undergoing IVF. *Int J Androl*. 2010;33(2):385-393.
203. Sugiura-Ogasawara M, Ozaki Y, Sonta S, Makino T, Suzumori K. Exposure to bisphenol A is associated with recurrent miscarriage. *Hum Reprod*. 2005;20(8):2325-2329.
204. Carwile JL, Luu HT, Bassett LS, et al. Polycarbonate bottle use and urinary bisphenol A concentrations. *Environ Health Perspect*. 2009;117(9):1368-1372.
205. Quaas A, Dokras A. Diagnosis and treatment of unexplained infertility. *Rev Obstet Gynecol*. 2008;1(2):69-76.
206. Jungwirth A, Diemer T, Copa Z, et al. European Association of Urology Guidelines on Male Infertility. Available at https://uroweb.org/eau-guidelines/discontinued-topics/male-infertility. Last accessed June 12, 2023.
207. Kolettis PN. Evaluation of the subfertile man. *Am Fam Physician*. 2003;67(10):2165-2172.
208. Dave CN, Dave A, Meier K, Bennett RC. Male Infertility. Available at https://emedicine.medscape.com/article/436829-overview. Last accessed June 12, 2023.
209. Vause TD, Cheung AP, Sierra S, et al. Ovulation induction in polycystic ovary syndrome. *J Obstet Gynaecol Can*. 2010;32(5):495-502.
210. Centers for Disease Control and Prevention. How Much Physical Activity Do Adults Need? Available at https://www.cdc.gov/physicalactivity/basics/adults/index.htm. Last accessed June 12, 2023.
211. Tonkin RS. Practical approaches to eating disorders in adolescence: primer for family physicians. *Can Fam Physician*. 1994;40: 299-304.

212. Santen FJ, Sofsky J, Bilic N, Lippert R. Mechanism of action of narcotics in the production of menstrual dysfunction in women. *Fertil Steril.* 1975;26(6):538-548.

213. Cicero TJ, Bell RD, Wiest WG, Allison JH, Polakoski K, Robins E. Function of the male sex organs in heroin and methadone users. *N Engl J Med.* 1975;292(17):882-887.

214. Schürmeyer T, Knuth UA, Belkien L, Nieschlag E. Reversible azoospermia induced by the anabolic steroid 19-nortestosterone. *Lancet.* 1984;1(8374):417-420.

215. Torpy JM, Burke AE, Glass RM. JAMA patient page: acute emotional stress and the heart. *JAMA.* 2007;298(3):360.

216. University of Adelaide. Potential Link Between IVF and Diabetes. Available at http://www.adelaide.edu.au/news/news41361.html. Last accessed June 12, 2023.

217. Legro RS, Arslanian SA, Ehrmann DA, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2013;98(12):4565-4592.

218. Nugent D, Vandekerckhove P, Hughes E, Arnot M, Lilford R. Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. *Cochrane Database Syst Rev.* 2000;(4):CD000410.

219. Roque M, Tostes AC, Valle M, Sampaio M, Geber S. Letrozole versus clomiphene citrate in polycystic ovary syndrome: systematic review and meta-analysis. *Gynecol Endocrinol.* 2015;31(12):917-921.

220. Legro RS. Ovulation induction in polycystic ovary syndrome: current options. *Best Pract Res Clin Obstet Gynaecol.* 2016;37:152-159.

221. Franik S, Eltrop SM, Kremer JA, Kiesel L, Farquhar C. Aromatase inhibitors (letrozole) for subfertile women with polycystic ovary syndrome. *Cochrane Database Syst Rev.* 2018;(5):CD010287.

222. Cheng J, Lv J, Li CY, Xue Y, Huang Z, Zheng W. Clinical outcomes of ovulation induction with metformin, clomiphene citrate and human menopausal gonadotrophin in polycystic ovary syndrome. *J Int Med Res.* 2010;38(4):1250-1258.

223. Nugent D, Vanderkerchove P, Hughes E, Arnot M, Lilford R. WITHDRAWN: Gonadotrophin therapy for ovulation induction in subfertility associated with polycystic ovary syndrome. *Cochrane Database Syst Rev.* 2015;(8):CD000410.

224. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2010;64(RR-03):1-137.

225. Nardo LG, Moustafa M, Beynon DW. Reproductive outcome after laparoscopic treatment of minimal and mild endometriosis using Helica Thermal Coagulator. *Eur J Obstet Gynecol Reprod Biol.* 2006;126(2):264-267.

226. Marcoux S, Maheux R, Bérubé S. Laparoscopic surgery in infertile women with minimal or mild endometriosis. Canadian Collaborative Group on Endometriosis. *N Engl J Med.* 1997;337(4):217-222.

227. Parazzini F. Ablation of lesions or no treatment in minimal-mild endometriosis in infertile women: a randomized trial. Gruppo Italiano per lo Studio dell'Endometriosi. *Hum Reprod.* 1999;14(5):1332-1334.

228. Crosignani PG, Vercellini P, Biffignandi F, Costantini W, Cortesi I, Imparato E. Laparoscopy versus laparotomy in conservative surgical treatment for severe endometriosis. *Fertil Steril.* 1996;66(5):706-711.

229. Chapron C, Vercellini P, Barakat H, Vieira M, Dubuisson JB. Management of ovarian endometriomas. *Hum Reprod Update.* 2002;8(6):591-597.

230. Schippert C, Bassler C, Soergel P, Hille U, Hollwitz B, Garcia-Rocha GJ. Reconstructive, organ-preserving microsurgery in tubal infertility: still an alternative to in vitro fertilization. *Fertil Steril.* 2010;93(4):1359-1361.

231. Ahmad G, Watson A, Vandekerckhove P, Lilford R. Techniques for pelvic surgery in subfertility. *Cochrane Database Syst Rev.* 2006;(2):CD000221.

232. Wurn BF, Wurn LJ, King CR, et al. Treating fallopian tube occlusion with a manual pelvic physical therapy. *Altern Ther Health Med.* 2008;14(1):18-23.

233. Amer SA, Li TC, Ledger WL. Ovulation induction using laparoscopic ovarian drilling in women with polycystic ovarian syndrome: predictors of success. *Hum Reprod.* 2004;19(8):1719-1724.

234. Amer SA, Li TC, Cooke ID. Repeated laparoscopic ovarian diathermy is effective in women with anovulatory infertility due to polycystic ovary syndrome. *Fertil Steril.* 2003;79(5):1211-1215.

235. Debras E, Fernandez H, Neveu ME, Deffieux X, Capmas P. Ovarian drilling in polycystic ovary syndrome: long term pregnancy rate. *Eur J Obstet Gynecol Reprod Biol X.* 2019;4:100093.

236. Kop PA, Mochtar MH, O'Brien PA, Van der Veen F, van Wely M. Intrauterine insemination versus intracervical insemination in donor sperm treatment. *Cochrane Database Syst Rev.* 2018;(1):CD000317.

237. American Society for Reproductive Medicine. Assisted Reproductive Technologies. Available at https://www.asrm.org/topics/topics-index/assisted-reproductive-technologies/. Last accessed June 12, 2023.

238. Sunkara SK, Rittenberg V, Raine-Fenning N, Bhattacharya S, Zamora J, Coomarasamy A. Association between the number of eggs and live birth in IVF treatment: an analysis of 400,135 treatment cycles. *Hum Reprod.* 2011;26(7):1768-1774.

239. Ye H, Huang GN, Gao Y, Liu de Y. Relationship between human sperm-hyaluronan binding assay and fertilization rate in conventional in vitro fertilization. *Hum Reprod.* 2006;21(6):1545-1550.

240. Nijs M, Creemers E, Cox A, et al. Relationship between hyaluronic acid binding assay and outcome in ART: a pilot study. *Andrologia*. 2010;42(5):291-296.

241. Min JK, Claman P, Hughes E, Society of Obstetricians and Gynaecologists of Canada, Canadian Fertility and Andrology Society. Guidelines for the number of embryos to transfer following in vitro fertilization. *J Obstet Gynaecol Can*. 2006;28(9):799-813.

242. Volgsten H, Skoog Svanberg A, Ekselius L, Lundkvist Ö, Sundström Poromaa I. Prevalence of psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. *Hum Reprod*. 2008;23(9):2056-2063.

243. Nelson CJ, Shindel AW, Naughton CK, Ohebshalom M, Mulhall JP. Prevalence and predictors of sexual problems, relationship stress, and depression in female partners of infertile couples. *J Sex Med*.2008;5(8):1907-1914.

244. Klemetti R, Raitanen J, Sihvo S, Saarni S, Koponen P. Infertility, mental disorders and well-being: a nationwide survey. *Acta Obstet Gynecol Scand*. 2010;89(5):677-682.

245. Shindel AW, Nelson CJ, Naughton CK, Ohebshalom M, Mulhall JP. Sexual function and quality of life in the male partner of infertile couples: prevalence and correlates of dysfunction. *J Urol*. 2008;179(3):1056-1059.

246. Chachamovich JLR, Chachamovich E, Ezer H, et al. Psychological distress as predictor of quality of life in men experiencing infertility: a cross-sectional survey. *Reprod Health*. 2010;7:3.

247. Ashkani H, Akbari A, Heydari ST. Epidemiology of depression among infertile and fertile couples in Shiraz, Southern Iran. *Indian J Med Sci*. 2006;60(10):399-406.

248. Schmidt L. Psychosocial consequences of infertility and treatment. *Reprod Endocrinol Infertility*. 2010;1:93-100.

249. Herbert DL, Lucke JC, Dobson AJ. Depression: an emotional obstacle to seeking medical advice for infertility. *Fertil Steril*. 2010;94(5):1817-1821.

250. Wilkins KM, Warnick JK, Serrano E. Depressive symptoms related to infertility and infertility treatments. *Psychiatr Clin North Am*. 2010;33(2):309-321.

251. Volgsten H, Skoog Svanberg A, Ekselsius L, Lundkvist Ö, Sundström Poromaa I. Risk factors for psychiatric disorders in infertile women and men undergoing in vitro fertilization treatment. *Fertil Steril*. 2010;93(4):1088-1096.

252. Lee SH, Wang SC, Kuo CP, Kuo PC, Lee MS, Lee MC. Grief responses and coping strategies among infertile women after failed in vitro fertilization treatment. *Scand J Caring Sci*. 2010;24(3):507-513.

253. Van den Broeck U, D'Hooghe T, Enzlin P, Demyttenaere K. Predictors of psychological distress in patients starting IVF treatment: infertility-specific versus general psychological characteristics. *Hum Reprod*. 2010;25(6):1471-1480.

254. Campagne DM. Should fertilization start with reducing stress? *Hum Reprod*. 2006;21(7):1651-1658.

255. Noorbala AA, Ramezanzadeh F, Abedinia N, Mehdi Naghizadeh M. Psychiatric disorders among infertile and fertile women. *Soc Psychiatry Psychiatr Epidemiol*. 2009;44(7):587-591.

256. Campagne DM. Stress: at what point in the medical treatment of infertility should it be treated? *Papeles del Psicólogo*. 2008;29(2):197-204.

257. Domar AD, Clapp D, Slawsby EA, Dusek J, Kessel B, Freizinger M. Impact of group psychological interventions on pregnancy rates in infertile women. *Fertil Steril*. 2000;73(4):805-811.

258. Hämmerli K, Znoj H, Barth J. The efficacy of psychological interventions for infertile patients: a meta-analysis examining mental health and pregnancy rate. *Hum Reprod Update*. 2009;15(3):279-95.

259. Faramarzi M, Alipor A, Esmaelzadeh, kheirkhah F, Poladi K, Pash H. Treatment of depression and anxiety in infertile women: cognitive behavioral therapy versus fluoxetine. *J Affect Disord*. 2008;108(1-2):159-164.

260. Hughes EG. Art therapy as a healing tool for sub-fertile women. *J Med Humanit*. 2009;31(1):27-36.

261. Haemmerli K, Znoj H, Berger T. Internet-based support for infertile patients: a randomized controlled study. *J Behav Med*. 2010;33(2):135-146.

262. Cousineau TM, Green TC, Corsini E, et al. Online psychoeducational support for infertile women: a randomized controlled trial. *Hum Reprod*. 2008;23(3):554-566.

263. Serafini P, Sabatini Lobo D, Grosman A, Seibel D, Rocha AM, Motta ELA. Fluoxetine treatment for anxiety in women undergoing in vitro fertilization. *Int J Gynaecol Obstet*. 2009;105(2):136-139.

264. Schmidt L, Holstein B, Christensen U, Boivin J. Does infertility cause marital benefit? An epidemiological study of 2250 women and men in fertility treatment. *Patient Educ Couns*. 2005;59(3):244-251.

265. Pasch LA, Dunkel-Schetter C, Christensen A. Differences between husbands' and wives' approach to infertility affect marital communication and adjustment. *Fertil Steril*. 2002;77(6):1241-1247.

Evidence-Based Practice Recommendations Citations

Gavin L, Moskosky S, Carter M, et al. Providing quality family planning services: recommendations of CDC and the U.S. Office of Population Affairs. *MMWR*. 2014;63(RR04):1-54. Available at https://www.cdc.gov/mmwr/pdf/rr/rr6304.pdf. Last accessed June 16, 2023.

Practice Committee of the American Society for Reproductive Medicine. Subclinical hypothyroidism in the infertile female population: a guideline. *Fertil Steril*. 2015;104(3):545-553. Available at https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/practice-guidelines/for-non-members/subclinical_hypothyroidism_in_the_infertile_female_population.pdf. Last accessed June 16, 2023.

Wall DJ, Reinhold C, Akin EA, et al. *ACR Appropriateness Criteria: Female Infertility*. Reston, VA: American College of Radiology; 2019. Available at https://acsearch.acr.org/docs/3093336/Narrative. Last accessed June 16, 2023.

Society of Obstetricians and Gynaecologists of Canada, Okun N, Sierra S. Pregnancy outcomes after assisted human reproduction. *J Obstet Gynaecol Can*. 2014;36(1):64-83. Available at https://www.jogc.com/action/showPdf?pii=S1701-2163%2815%2930685-X. Last accessed June 16, 2023.

National Collaborating Centre for Women's and Children's Health. *Fertility: Assessment and Treatment for People with Fertility Problems*. London: National Institute for Health and Clinical Excellence; 2017. Available at https://www.nice.org.uk/guidance/cg156. Last accessed June 16, 2023.