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family history of breast cancer in a first-degree relative or other contraindications, and who have a strong personal preference for therapy. Poor candidates are women with elevated cardiovascular risk, those at increased risk of breast cancer, and those at low risk of osteoporosis. Even for reasonable candidates, strategies to mini mize dose and duration of use should be employed. For example, women using HT to relieve intense vasomotor symptoms in early postmenopause should consider discontinuing therapy within

5 years, resuming it only if such symptoms persist. Because of the role of progestogens in increasing breast cancer risk, regimens that employ cyclic rather than continuous progestogen exposure as well as formulations other than MPA should be considered if treatment is extended. For prevention of osteoporosis, alternative therapies such as bisphosphonates or SERMs should be considered. Research on alternative progestogens and androgen-containing preparations has been limited, particularly with respect to long-term safety. Additional research on the effects of these agents on cardiovascular disease, glucose tolerance, and breast cancer will be of particular interest. For genitourinary symptoms such as vaginal dryness or pain with intercourse/sexual activity, intravaginal estrogen creams, tablets, or rings; prasterone (vaginal dehydroepiandrosterone); and ospemi fene are options. Contraindications to low-dose vaginal estrogen include unexplained vaginal bleeding or breast cancer, endometrial cancer, or other estrogen-dependent cancer. Contraindications to ospemifene and prasterone are the same as those for low-dose vaginal estrogen, and contraindications for ospemifene additionally include venous or arterial thromboembolic disease, severe liver dis ease, and use of estrogens or estrogen agonists-antagonists. In addition to HT, lifestyle choices such as smoking abstention, adequate physical activity, and a healthy diet can play a role in con trolling symptoms and preventing chronic disease. An expanding array of pharmacologic options (e.g., bisphosphonates, SERMs, and other agents for osteoporosis; cholesterol-lowering or antihyper tensive agents for cardiovascular disease) should also reduce the widespread reliance on hormone use. However, short-term HT may still benefit some women. ■ ■FURTHER READING Bassuk SS, Manson JE: Menopausal hormone therapy and cardiovas cular disease risk: Utility of biomarkers and clinical factors for risk stratification. Clin Chem 60:68, 2014. Chlebowski RT et al: Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women’s Health Initiative randomized clinical trials. JAMA 324:369, 2020. Crandall CM et al: Management of menopausal symptoms: A review. JAMA 329:5, 2023. Duralde ER et al: Management of perimenopausal and menopausal symptoms. BMJ 382:e072612, 2023. Manson JE, Bassuk SS: Hot

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Infertility and

Contraception INFERTILITY The World Health Organization (WHO) categorizes infertility as a disease of the reproductive system. Infertility is the third most com mon disease worldwide, affecting ~48–72 million couples. It is defined as the inability to achieve a pregnancy over 12 months of unprotected intercourse. The prevalence of infertility, ~17.5% globally, has remained relatively stable over the past few decades. Primary infertility occurs in couples who have never achieved a pregnancy, whereas secondary infer tility refers to infertility after achieving at least one pregnancy. During the first year of attempting pregnancy, the fecundability rate, defined as the ability to achieve a pregnancy within one menstrual cycle, is highest in the first 3 months and declines over the next 9 months. Approximately 85% of couples will achieve pregnancy after 12 months, and 95% will achieve pregnancy after 24 months. Increasing trends toward later child bearing can have significant implications due to age-related decrease in the fecundability rate. Compared to women aged 30–31 years of age, fecundability is reduced by 14% in women aged 34–35 years, 19% in women aged 36–37 years, 53% in women aged 40–41 years, and 59% in women aged 42–44 years. Infertility and Contraception CHAPTER 408 ■ ■ETIOLOGY The causes for infertility are generally classified as female factors, male factors, and unexplained infertility (Fig. 408-1). The female causes include tubal factors (pelvic inflammatory disease, endometriosis, prior surgery, salpingitis isthmica nodosum), uterine etiology (fibroids, congenital malformations, uterine scarring), ovulatory dysfunction (polycystic ovary syndrome [PCOS], diminished ovarian reserve, pre mature ovarian insufficiency), and endocrine dysfunction (hypothy roidism, hyperprolactinemia). Although the probability of achieving a pregnancy decreases after the age of 35 in women, primarily due to chromosomal abnormalities in the oocyte during meiosis, a similar decline has not been observed in men <50 years of age. The male causes of infertility include anatomic factors in the reproductive system (vasectomy, infection, absence of the vas), endocrine factors (hypogo nadotropic hypogonadism, hypothyroidism, hyperprolactinemia, mor bid obesity, use of certain medications), sexual dysfunction (erectile or ejaculatory dysfunction, decreased libido), and genetic factors con tributing to primary testicular dysfunction, including defects in sper matogenesis (Klinefelter's syndrome, Y chromosome microdeletions). The distribution of these causes varies significantly across the world. Overall, female factors are present in 30–40% of couples with infertility, male factors are present in 40–50%, and both male and female factors are identified in 20–30%. Unexplained infertility refers to the absence of any identified abnormality after completing the fertility workup and occurs in up to 30% of couples. As a result, a complete workup of both partners is recommended in all couples presenting with infertility. ■ ■FERTILITY

EVALUATION Diagnostic evaluation for infertility is typically initiated after 1 year of unprotected intercourse because 80–85% of couples will achieve a pregnancy over this time period. Evaluation can be initiated even prior to meeting the definition of infertility, especially if one of the partners has risk factors for infertility. If the female partner's age is

> 35 years, it is recommended to initiate evaluation after 6 months of attempting pregnancy. If the age of the female partner is >40 years, it is recommended to start evaluating the couple immediately. The initial evaluation should include detailed medical history, laboratory testing, radiologic evaluation, and preconception counseling for both partners. As multiple causes for infertility may be identified, it is best to perform the complete diagnostic evaluation prior to initiating treatment.

Causes of infertility 12–15% of reproductive aged women Unexplained 15–30% Male causes 40–50% Female causes 30–40% Endocrine Anatomic Testicular defects/ genetic PART 12 Endocrinology and Metabolism Uterine Other Tubal Ovulatory dysfunction Endocrine FIGURE 408-1 Causes of infertility. History and Physical Exam A detailed history obtained from both partners is essential to identify risk factors for infertility. In the female partner, gynecologic history (menstrual frequency, menorrhagia, dys menorrhea, history of sexually transmitted infections, endometriosis), medical and endocrine history, exposure to pelvic radiation, abdominal or pelvic surgeries, tobacco and alcohol use, medication use including cytotoxic drugs, family history of early menopause, and prior history of pregnancy should be assessed. In addition, frequency of intercourse, timing of intercourse, use of methods to detect ovulation, and concerns regarding sexual dysfunction over the past several months should be ascertained. Physical exam in the female partner should include assess ment of weight and blood pressure (BP), thyroid and breast exam, assessment for signs of hyperandrogenism, and pelvic exam to assess uterine size, adnexal masses, and factors that might impact intercourse. Similarly, a detailed history should be obtained in the male partner with specific questions regarding injuries and surgery in the reproductive tract; mumps orchitis; exposure to pelvic radiation; use of androgens, cytotoxic drugs, and other medications; and fertility with any prior partner. The exam in the male partner should include body mass index (BMI), BP, and complete physical exam including testicular exam. Ultrasound An abdominal and transvaginal pelvic ultrasound can assess uterine (myomas, adenomyosis, müllerian anomalies) and adnexal abnormalities (endometriosis, polycystic-appearing ovaries) and evalu ate ovarian reserve (number of antral follicles in both ovaries). Ovulation Assessment Women who have regular menstrual cycles between 25 and 35 days will typically have ovulatory cycles. Ovulation can be assessed by using ovulation detection strips at home to detect urinary luteinizing hormone (LH) or by measuring a serum progesterone level 7 days after ovulation. Basal body temperatures can also be used to confirm ovulation when a rise in temperature is noted in the luteal phase. However, basal body temperature measurements are less reliable than the above methods. Hysterosalpingogram An hysterosalpingogram (HSG) is per formed during the follicular phase to assess the patency of fallopian tubes by injecting radiopaque contrast through the cervix into the uterus and imaging the flow of contrast through one or both tubes. In addition to identifying tubal pathology, an HSG may identify intrauter ine abnormalities such as polyps, submucosal myomas, and adhesions. Although the negative predictive value of HSG for assessing tubal patency is high, the positive predictive

value is relatively low. Interest ingly, pregnancy rates have been shown to be higher after an HSG test compared to no testing and higher when oil-based contrast was used compared to water-based contrast, likely related to tubal flushing of mucus plugs. Alternate options that are increasingly used include injection of agitated saline contrast through the cervix into the uterus. Tubal patency is assessed by demonstrating passage of agitated saline

Unknown contrast through the tubes or accumulation in the cul de sac as visual ized by ultrasonography. A saline infusion sonogram is more accurate in assessing intrauterine pathology such as polyps and intrauterine scarring compared to HSG and can be combined with ultrasound assessment of the pelvis. Ovarian Reserve Evaluation Assessment of ovarian reserve includes measurement of serum FSH and estradiol on day 2 or 3 of the menstrual cycle and serum anti-müllerian hormone (AMH). These screening tests combined with age of the female partner and antral fol licle counts measured by ultrasound can identify diminished ovarian reserve and provide information on the urgency to initiate treatment. AMH and antral follicle counts are also used to determine starting doses of gonadotropins for fertility treatments. These markers of ovar ian reserve, however, do not predict the likelihood of pregnancy and live birth. Endocrine Tests In women with irregular menses, serum TSH, prolactin, and androgens (total and free testosterone) should be mea sured to identify other causes for anovulation. Semen Analysis (see Chap. 403) The semen sample is collected after 2–7 days of abstinence and provides an assessment of sperm count, motility, morphology, volume, and pH. None of the individual sperm parameters are predictive of fertility, but the likelihood of infertility increases with multiple abnormalities. Those with abnormal sperm parameters based on the WHO criteria (oligoasthenozoosper mia is defined as sperm counts <15 million/mL, motility <40%, and normal morphology <4%) should have a physical exam and endocrine evaluation (serum follicle-stimulating hormone [FSH], LH, prolactin, and thyroid-stimulating hormone [TSH]); those with azoospermia or severe oligospermia (<5 million/mL) should have genetic evalua tion (karyotype and Y chromosome microdeletion). Although a DNA sperm fragmentation assay is not part of the initial evaluation, it may be indicated in patients with recurrent pregnancy loss. Sperm antibody testing and scrotal ultrasound should not be routinely performed in infertile men. Genetic Screening All couples can be offered preconception genetic screening based on ethnicity, family history, or common auto somal recessive conditions. Of note, diagnostic laparoscopy, postcoital test, endometrial biopsy, thrombophilia, and immunologic testing and karyotype are not indi cated as part of the initial workup of infertility. ■ ■COUNSELING AND TREATMENT Preconception Counseling All patients seeking fertility care should be provided with preconception counseling to identify modifi able risks and optimize pregnancy outcomes. This includes counseling

about eating disorders or lifestyle modifications for weight manage ment as obesity in women is associated with an increase in anovulatory cycles, miscarriage rates, and maternal and fetal complications in preg nancy. Obesity in men is associated with abnormal sperm parameters. Preconception counseling regarding smoking cessation is important as evidence suggests that smoking cessation can reverse the detrimental impact of smoking on fecundity. Smoking decreases fertility rates by a direct impact on oocyte DNA and also increases the risk of miscar riage and ectopic pregnancy. In addition, smoking during pregnancy is associated with an increased risk of placental abruption and intrauter ine growth restriction (IUGR). Moreover, the impact of smoking on ovarian reserve has been shown to accelerate the time to menopause by 1–4 years. As high levels of caffeine consumption increase the risk of infertility and miscarriage, women should be counseled

to restrict caffeine consumption to ≤2 cups while attempting pregnancy and during pregnancy. Use of testosterone products, which are widely used for the treatment of hypoandrogenism and sexual dysfunction in men, should be stopped. Inquiries should be made about possible misuse of androgens for physical appearance or performance enhancement (Chap. 411). As part of the preconception counseling, patients should be informed that the fertile window is typically 5–6 days prior to ovula tion, and therefore, intercourse every 1–2 days during this time period will increase the chance of pregnancy. Various methods are used by women to detect ovulation, including basal body temperature measure ments, assessment of changes in cervical mucus, and urinary LH kits. A rise in basal body temperatures indicates that ovulation has occurred and therefore cannot be used to time intercourse. LH kits can be used to detect the start of ovulation and subsequently time intercourse on the day of the LH surge and the following day. Physicians should coun sel patients that advanced maternal age (>35 years) is associated with a higher risk of aneuploidy and advanced paternal age (>40 years) is associated with adverse health outcomes in the offspring. Treatment Treatment recommendations depend on the results of the fertility evaluation described above (Table 408-1). The success of different treatments depends on several factors including age of the female partner, assessment of ovarian reserve, history of smoking, BMI, and race. Tubal Factor Infertility Tubal factor infertility constitutes 30–35% of cases of female infertility, and a large majority are second ary to tubal obstruction resulting from sexually transmitted infections. In vitro fertilization (IVF) was first developed as a treatment for tubal factor infertility as it bypasses the fallopian tubes and allows fertiliza tion of oocytes in the laboratory prior to transcervical transfer into the uterus. IVF offers the highest success rates for couples with tubal factor infertility. Tubal repair or reconstruction is typically not recommended in cases associated with tubal infections or hydrosalpinx, due to both TABLE 408-1 Assisted Reproductive Technologies Ovulation induction Oral agents Injectable hormones Clomiphene citrate (selective estrogen response modulator) Letrozole (aromatase inhibitor) FSH, LH (gonadotropins) Intrauterine insemination (IUI) Office-based procedure by which washed and concentrated ejaculated sperm is deposited in the uterine cavity via a soft catheter passed through the cervix In vitro fertilization (IVF) Oocytes are harvested transvaginally under local anesthesia or intravenous sedation and incubated with sperm to facilitate fertilization. The fertilized embryos are cultured for 3 days (cleavage stage) or 5 days (blastocyst stage) prior to transcervical placement of one or more embryos, depending on the age of the female patient, into the uterine cavity under ultrasound guidance. Intracytoplasmic sperm injection (ICSI) In cases of severe male factor infertility, a single motile morphologically normal appearing sperm is injected into the oocyte for potential fertilization. Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

the low success rate in achieving tubal patency and increased risk of ectopic pregnancy. In fact, removal of hydrosalpinges by salpingec tomy will improve pregnancy rates in subsequent IVF treatments as it prevents efflux of tubal fluid into the uterine cavity. If a proximal tubal blockage is observed on HSG, radiographically guided cannulation of fallopian tubes can be attempted. In women with bilateral tubal liga tion, the decision between microsurgical reanastomosis versus IVF will depend on a number of factors including patient’s age, ovarian reserve, number of children desired, partner’s semen parameters, experience of the surgeon, and cost of procedure.

Infertility and Contraception CHAPTER 408 Ovulatory Dysfunction Endocrine conditions such as hypo thyroidism and hyperprolactinemia should be treated prior to use of ovulation induction medications. Lifestyle modifications should be recommended in patients with low BMI or obesity.

Weight loss in obese women has been shown to increase the likelihood of spontaneous or drug-induced ovulation. First-line treatment for anovulatory infertility (most common etiology is PCOS) includes use of letrozole followed by clomiphene citrate to induce ovulation (Chap. 406). A large majority of women with PCOS (60–80%) respond to these oral medications, and the addition of metformin, combined with the above medications as a second-line agent, may further increase the chance of ovulation, particularly in obese women. In women with hypothalamic amenor rhea, behavioral modifications such as weight gain and decreased exercise may resume ovulation. If there is no response, judicious use of low-dose injectable gonadotropins can induce monofollicular growth. In women with diminished ovarian reserve, treatment can be esca lated from ovulation induction with oral medications and intrauterine insemination (IUI) to IVF, as the overall live birth rates are lower. In both women with diminished ovarian reserve and women with pre mature ovarian insufficiency, the option of using donor oocytes can be offered. In that case, the egg donor will undergo the IVF procedure, the harvested eggs are fertilized with the male partner's sperm, and the fertilized embryos will be transferred to the patient's uterus. Male Infertility Given the high prevalence of male factor infertil ity (40–50%), timely evaluation and treatment are recommended. Men with abnormal semen parameters have associated health risks and should have a detailed evaluation by specialists in male reproduction. In men with no sperm (azoospermia) in the ejaculate, further evaluation including a repeat semen analysis followed by physical examination, endocrine tests, and genetics studies should be performed to identify obstructive (40% prevalence) versus nonobstructive etiology. First-line treatment for mild to moderate male factor infertility includes IUI alone or IUI combined with ovulation induction, depending on the female partner's age and other causes of infertility. In men with severe male factor infertility (sperm count <5 million/mL or motility <20%), IVF with intracytoplasmic sperm injection (ICSI) is recommended. In men with obstructive azoospermia, sperm can be procured by direct aspiration from the epididymis or testis. In men with congenital bilateral absence of the vas deferens (CBAVD), testing for CFTR muta tions and genetic counseling are indicated before to offering IVF with ICSI. In men with nonobstructive azoospermia, microsurgical sperm retrieval from the testes may result in successful pregnancies after IVF-ICSI; however, the use of donor sperm for IUI is an alternate option. Men with hypogonadotropic hypogonadism (e.g., Kallmann's syndrome) can be treated with gonadotropins to initiate spermatogen esis followed by IUI or IVF. Treatment of male sexual dysfunction and avoidance of exogenous androgens are effective strategies for address ing male factor infertility. Repair of a moderate to large varicocele is recommended when associated with abnormal semen parameters or if the patient is symptomatic from the varicocele; however, it may take several months to detect an improvement in semen parameters. Unexplained Infertility In 15–30% of couples, no clear causes of infertility are identified. In such cases, it is appropriate to initiate ovarian stimulation with oral medications to increase the number of developing oocytes combined with IUI timed to ovulation in order to increase the number of motile sperm in the reproductive tract. Depending on the age of the female partner, this approach offers

modest success rates limiting its use to 3–6 months before recommend ing IVF. Overall, IVF is associated with a low risk of complications; the risk of ovarian hyperstimulation syndrome is significantly decreased by judiciously monitoring stimulation and using gonadotropin-releasing hormone (GnRH) to trigger ovulation instead of human chorionic gonadotropin (hCG). Multiple pregnancy remains the highest risk associated with IVF despite improvements in cryopreservation of embryos and age-based guidelines for limiting the number of embryos to transfer. In some couples, the IVF treatment may reveal an underly ing cause of infertility such as lower fertilization,

embryo cleavage, or blastocyst formation rates. Of note, guidelines from different medical societies around the world vary in the rapidity of offering IVF for unexplained infertility.

PART 12 Endocrinology and Metabolism Uterine Factors Fibroids are the most common benign tumors of the reproductive tract and occur in 50–70% of reproductive-age women. It is not clear whether fibroids decrease the likelihood of pregnancy; submucosal fibroids and intramural fibroids that distort the endometrial cavity may lower pregnancy rates and increase the risk of pregnancy loss. Removal of submucosal fibroids, uterine polyps, and intrauterine adhesions hysteroscopically may improve subsequent pregnancy rates. Endometriosis Endometriosis is a common gynecologic condition associated with pelvic pain and dysmenorrhea, and in severe cases, it is associated with tubo-ovarian infertility. Approximately 25–50% of infertile women have endometriosis, and 30–50% of women with endometriosis have infertility. Prolonged medical management to suppress endometriotic lesions and surgical treatment of stage 1 and 2 endometriosis have not been shown to improve subsequent fertility rates. Surgical removal of endometriotic lesions or endometriomas in women with stage 3 or 4 endometriosis may improve subsequent pregnancy rates. First-line treatment of infertility associated with endometriosis alone includes use of oral ovulation induction medica tions and IUI. ■ ■PSYCHOLOGICAL ASPECTS OF INFERTILITY It is well recognized that infertility is associated with psychological stress related not only to the diagnostic and therapeutic procedures themselves but also to repeated cycles of hope and loss associated with each new procedure or cycle of treatment that does not result in the birth of a child. These feelings are often combined with a sense of isolation from friends and family. Counseling and stress-management techniques should be offered early in the evaluation of infertility as many patients do not pursue treatments after the initial consultation. Importantly, infertility and its treatment do not appear to be associated with long-term psychological sequelae. CONTRACEPTION The desired ideal number of children per family varies around the globe and is approximately 2.6 in the United States. Couples not using any form of contraception have an 85% chance of achieving a pregnancy over 1 year. Based on these data, couples spend most of their reproductive life preventing a pregnancy and a much smaller proportion attempting to become or being pregnant. It is therefore not surprising that a majority of women who have been sexually active will have used some form of contraception to prevent a pregnancy. Unin tended pregnancies primarily occur due to lack of use or inconsistent use of contraceptives rather than failure of the contraceptive method used. Of the different forms of contraception used worldwide in 2022, tubal sterilization was the most common (~219 million) followed by use of male condom (208 million), intrauterine device (IUD) (161 mil lion), and the (birth control) pill (150 million). Contraceptive methods used by married women differ from those used by single women, and the most widely used contraceptive methods differ by world regions. The rates of female sterilization increased steadily in the last century and now show a slight decrease, likely due to the increasing use of long-acting reversible contraceptive (LARC) agents, such as IUDs and implants, which are as effective as sterilization. The convenience of use of contraceptives determines their compliance and efficacy;

TABLE 408-2 U.S. Medical Eligibility Criteria (USMEC) for Contraceptive Use USMEC Category 4 (a condition that represents an unacceptable health risk if the contraceptive method is used) Smoking: women age ≥35 years who smoke ≥15 cigarettes per day Known ischemic heart disease or multiple risk factors for cardiovascular disease (older age, smoking, diabetes, low HDL, high LDL, high triglycerides, and hypertension) Acute DVT Previous thromboembolic event; high risk of recurrent DVT Stroke or known thrombogenic mutations Complicated valvular heart disease

Peripartum cardiomyopathy (<6 months, moderately to severely impaired cardiac function) Complicated solid organ transplantation Hypertension (systolic ≥160 mmHg or diastolic ≥100 mmHg, vascular disease) Systemic lupus erythematous (positive or unknown antiphospholipid antibodies) Cirrhosis, hepatocellular adenoma or hepatoma (malignant) Viral hepatitis, acute flare Pregnancy and early postpartum (<21 days) Breast-feeding <21days postpartum Breast cancer Diabetes: neuropathy/retinopathy/nephropathy Migraines with aura USMEC Category 3 (a condition for which the theoretical or proven risks outweigh the advantages for using the method) Smoking: women ≥35 years who smoke <15 cigarettes/day Previous thromboembolic event; lower risk of recurrent DVT Superficial thrombosis (acute or history of) Past history of breast cancer and no evidence for 5 years Hypertension (adequately controlled or systolic 140–159 mmHg or diastolic 90–99 mmHg) Anticonvulsant drug therapy (certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine) Antimicrobial therapy: rifampin or rifabutin Antiretroviral therapy for prevention (preexposure prophylaxis) or treatment of HIV Bariatric surgery (Roux-en-Y gastric bypass or biliopancreatic diversion) Breast-feeding 21–42 days postpartum with or without risk factors for VTE Abbreviation: DVT, deep-vein thrombosis; HDL, high-density lipoprotein; LDL, lowdensity lipoprotein; VTE, venous thromboembolism. contraceptives requiring daily and coitus-related use have higher fail ure rates compared to long-acting reversible and permanent methods. The U.S. Medical Eligibility Criteria (USMEC) for contraceptive use are evidence-based guidelines to help health care providers recom mend appropriate contraceptives to women with chronic medical conditions (Table 408-2). This excellent resource is adapted from the WHO guidance and is kept up to date through continual review of published literature. ■ ■TYPES OF CONTRACEPTION These can be classified in a number of ways, such as permanent versus reversible, hormonal versus nonhormonal, or barrier versus nonbarrier (Table 408-3). Permanent Contraception The permanent forms of contracep tion include tubal sterilization and vasectomy. Male sterilization has declined globally with a rate of <2% in 2022. Vasectomy is a low-risk procedure typically performed in an outpatient setting with a very low failure rate of 0.1 pregnancies per 100 women per year. It is not immediately effective, and patients should be told to use other forms of contraception for a minimum of 3 months after the procedure. Glob ally, tubal sterilization rates have also declined steadily and represent 23% of all methods. Tubal sterilization can be performed in the post partum period or as an interval procedure and has a failure rate of 0.5 pregnancies per 100 women per year. Postpartum sterilization can be

TABLE 408-3 Effectiveness of Different Forms of Contraception THEORETICAL EFFECTIVENESS (%) ACTUAL EFFECTIVENESS (%) METHOD OF CONTRACEPTION No method

34.7 Fertility awareness

1.2 Withdrawal

4.4 Barrier methods Condoms

8.4 Diaphragm

Spermicides

Sterilization Female 99.5 99.5

18.1 Male 99.5 99.9

5.6 Intrauterine device 10.4 Copper T 99.4 99.8

Progestin-containing 99.8 99.8

Hormonal contraceptives Combined and progestin only 99.7

Transdermal patch 99.7

0.5 Vaginal ring 99.7

1.8 Implant 3.1 Depo-Provera 99.8

Subdermal implant 99.5 99.5

Emergency contraception

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Sources: Data from J Trussell et al: Contraceptive Efficacy, in Contraceptive Technology, 20th revised ed. RA Hatcher et al (eds). New York, Ardent Media, 2011; CDC. NCHS National Survey of Family Growth, 2011-2013; J Jones et al: Current contraceptive use in the United States, 2006-2010, and changes in patterns of use since 1995. Natl Health Stat Report 60:1, 2012; and NE Birgisson et al: Preventing unintended pregnancy: The contraceptive CHOICE project in review. J Womens Health (Larchmt) 24:349, 2015. Current Contraceptive Status Among Women Aged 15–49: United States, 2017–2019 NCHS Data Brief No. 388, October 2020. Available at: https://www.cdc.gov/nchs/ products/databriefs/db388.htm. performed during a cesarean section or after a vaginal delivery via minilaparotomy. Interval procedures can be performed laparoscopically or via mini-laparotomy and include partial or complete salpingectomy or occlusion of the fallopian tubes using electrocoagulation or mechanical devices such as clips. These permanent methods of contraception are highly effective as they avoid the need for user-dependent contracep tion. All patients should undergo preprocedure counseling regarding risk of failure, permanence of the procedure, regret, and alternatives. Hormonal Contraceptives • COMBINED ESTROGEN- AND PROGESTIN-CONTAINING CONTRACEPTIVES The mechanism of action of the hormonal contraceptives involves negative feedback from continuous estrogen administration, thereby decreasing FSH secre tion, follicular development, and formation of a dominant follicle. The continuous progestin suppresses LH secretion and inhibits ovulation, alters endometrial receptivity, thickens the cervical mucus, and impairs tubal motility. These hormones can be delivered via oral pills to be taken daily, as a transdermal patch that is changed weekly, or a vaginal ring that is replaced monthly or annually. There are numerous pills available containing different doses of estrogen (<50 µg) and types of estrogen and progestins and varying doses within a pack (monophasic vs multiphasic); the pills can be taken in a cyclic or extended cycle schedule. The contraceptive efficacy is similar with varying doses of estrogen and progestin. Decreasing the duration of hormone-free days may decrease some side effects associated with menses, such as men strual migraines and dysmenorrhea. The overall failure rate for com bined hormonal

contraceptives is 8 pregnancies per 100 women per year, although compliance with daily use of pills may be lower, affecting efficacy. The contraceptive patch and vaginal ring have higher compli ance compared to daily pills. Use of the contraceptive patch is associ ated with a low risk of skin reactions and a lower efficacy in women weighing >90 kg. The transdermal mode of delivery is associated with a higher steady state comparable to that of a 40-µg ethinyl estradiol oral contraceptive. Hormonal contraceptives offer additional benefits such as regulation of menstrual cycles; suppression of ovarian cysts; and decrease in menorrhagia, dysmenorrhea, and hyperandrogenism

CONTINUED USE AT 1 YEAR (%) USE OF CONTRACEPTIVE METHOD BY U.S. WOMEN AGE 15–49 (%) Infertility and Contraception CHAPTER 408 symptoms; in addition, they reduce the risk of both endometrial (50% reduction) and ovarian cancer (40% reduction). Common side effects include nausea, breast tenderness, bloating, and intermenstrual bleeding. There may be a mild increase in BP in some patients, and it is recommended to check BP at follow-up visits. In large studies and meta-analyses, hormonal contraceptives are not associated with sig nificant weight gain, mood changes, or effect on libido. Prior to admin istering hormonal contraceptives, a detailed patient history should be obtained to determine any absolute or relative contraindications to their use. Due to the low but slightly increased risk of deep-vein throm bosis (DVT) associated with estrogen-containing hormonal contracep tives (3–15 per 10,000 women-years), they are contraindicated in the immediate postpartum period, in smokers over the age of 35 years, and in women with a history of hereditary thrombophilias or DVT. The association between risk of DVT and different doses of estrogen (ethi nyl estradiol <35 µg) or different routes of administration (transdermal patch) is weak. There is, however, some association between third- and fourth-generation progestins and increased risk of DVT. Routine screening for familial thrombotic disorders is not recommended prior to prescribing hormonal contraceptives. Although obesity is associated with decreased fertility, the vast majority of women with obesity do not experience infertility. The USMEC classifies obesity alone as risk category 2, where the benefits of taking hormonal contraceptives out weigh any theoretical risk. PROGESTIN-ONLY HORMONAL CONTRACEPTION Different types of progestins are used for contraception in oral pills, injectable forms, subdermal implants, and IUDs and may be an option for women who have contraindications to the use of estrogen-containing contracep tives (e.g., migraine with aura, DVT, stroke, breast-feeding). The failure rate with progestin-only pills is 9 pregnancies per 100 women per year, whereas the failure rate of progestin IUDs is 0.1 pregnan cies per 100 women per year. In addition to acting as a spermicidal, the levonorgestrel IUD also thickens the cervical mucus and thins the endometrium, thereby decreasing its receptivity. The common side effects include irregular bleeding, acne, breast tenderness, and pain,

with higher rates of expulsion when IUDs are inserted in the immedi ate postpartum period. Breakthrough bleeding or unscheduled bleed ing is commonly reported, as estrogen usually serves to stabilize the endometrial lining and prolonged exposure to progestin alone results in a thinner decidualized lining. Depending on the device used, the progestin IUD is effective for 3–7 years. The injectable form of proges terone (medroxyprogesterone acetate) is administered intramuscularly or subcutaneously every 3 months with a failure rate of 3 pregnancies per 100 women per year. Its side effects include weight gain, irregular menses, amenorrhea, and mood changes, and there is a slow return to ovulation and fertility after discontinuation (6–9 months). The subder mal implant contains etonogestrel and is placed easily over the triceps muscle in the inner arm using local

anesthesia. It lasts up to 5 years and has a failure rate of 0.05 pregnancies per 100 women per year. Findings from the Contraceptive Choice research project showed that continu ation rates were higher for LARC (IUDs and implants) compared to short-acting methods. LARCs are the most effective reversible form of contraception with high continuation and satisfaction rates; hence, they are a good choice in adolescents and nulliparous women.

PART 12 Endocrinology and Metabolism Nonhormonal IUD IUDs are a commonly used form of contra ception worldwide and are available as hormonal and nonhormonal devices. The nonhormonal copper IUD works as a spermicidal and is effective for up to 12 years with a failure rate of <1 pregnancy per 100 women per year. Patients should be counseled regarding the increased risk of heavy vaginal bleeding and dysmenorrhea resulting in higher discontinuation rates compared to the levonorgestrel-containing IUDs. IUDs can be used in adolescents and adult women and are typically inserted and removed as an office procedure with use of mild analge sics. They can be inserted anytime during a menstrual cycle, referred to as interval insertion, and in the immediate postpartum and postabor tion period. Barrier Contraception The barrier forms of contraception include condoms (male, female) and diaphragm and cervical cap and have lower effectiveness secondary to inconsistent and incorrect use. They offer several advantages including minimal side effects, lower cost, no requirement for a prescription, and protection from sexually transmitted infections. The failure rate for male and female condoms is 17–21 pregnancies per 100 women per year. Spermicidals can be used in conjunction with barrier methods to improve effectiveness. Lactational Contraception Lactation may serve as an effective form of contraception during the first 6 postpartum months if there is exclusive breast-feeding and menstrual cycles have not resumed. The contraceptive effect occurs due to suppression of GnRH pulsatility associated with suckling. The failure rate under these circumstances can be as low as 0.5–1.5 pregnancies per 100 women per year. Fertility Awareness The standard days method is typically used by women with regular menstrual cycles whereby they track their cycles to avoid intercourse from cycle days 8–19. The rhythm and withdrawal method are also referred to as traditional methods of contraception. Emergency Contraception Also known as postcoital contracep tion, this method is used after an unprotected or inadequately pro tected act of intercourse. The probability of pregnancy independent of the time of the month is 8%, but the probability varies significantly in relation to proximity to ovulation and may be as high has 30%. Many women are not aware of the availability of emergency contraception and its appropriate use. As the probability of pregnancy is highest if there has been unprotected intercourse during the 3 days prior to ovulation, the timing of administration and type of emergency contraceptive used determine the efficacy. Emergency contraception options include the copper IUD and oral medications such as ulipris tal acetate, levonorgestrel, and combined hormonal pills. The copper IUD prevents fertilization and implantation and is the most effective choice if inserted within 5 days of unprotected intercourse. It can be offered to obese women in whom other hormonal forms of emergency contraceptive may be less effective. Ulipristal acetate, a progesterone receptor antagonist, blocks the ability of endogenous progesterone to

act on its receptors and inhibits the LH surge, delaying or inhibiting ovulation, and may directly inhibit follicular rupture. It is administered as a 30-mg single dose up to 5 days after unprotected intercourse. Levonorgestrel administered as a single dose will prevent or delay ovu lation and is associated with fewer side effects compared to combined hormonal pills. Overall, the failure rate for all hormonal emergency contraception is 1–3%, with ulipristal acetate being the most effective. Side effects are mild and may include nausea, irregular vaginal bleed ing, and fatigue. Emergency

contraception should be offered to all women who ask for it up to 5 days after unprotected intercourse and not delayed in order to obtain a pregnancy test or perform a clinical examination. Although body weight can affect the efficacy of emer gency hormonal contraception, treatment should not be withheld from overweight and obese women. ■ ■CONTRACEPTION COUNSELING Patients should be provided information regarding the different meth ods of contraception, side effects, noncontraceptive benefits, efficacy, need for strict compliance, and impact on future fertility. In order to facilitate patient-centric care, the provider should discuss plans for future pregnancy and whether childbearing is complete. A detailed patient history should be reviewed to identify potential contraindica tions such as migraines with aura, smoking, and hypertension. Pro viders should refer to the most updated USMEC or WHO Medical Eligibility Criteria for Contraceptive Use guidelines when counseling patients with associated comorbidities. As part of the shared decisionmaking approach, the patient's choice should be the guiding factor, and the discussion should be nonjudgmental. Adolescents should be offered access to the full range of contraceptive options. In a low-risk patient, hormonal contraceptives can be prescribed from menarche to menopause; regular evaluation of side effects and assessment of changes in the patient's medical history, however, are required. ■ ■FURTHER READING American College of Obstetricians and Gynecologists: Effec tiveness of birth control. Available at https://www.acog.org/womenshealth/infographics/effectiveness-of-birth-control-methods. Accessed June 30, 2024. Centers for Disease Control and Prevention: Reproduc tive health. Available at https://www.cdc.gov/reproductivehealth/ Infertility/#e. Accessed November 22, 2023. Curtis KM, Peipert JF: Long-acting reversible contraception. N Engl J Med 376:461, 2017. Curtis KM et al: U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm Rep 65:1, 2016. Infertility Workup for the Women's Health Specialist: ACOG Committee Opinion, Number 781. Obstet Gynecol 133:e377, 2019. Reaffirmed in February 2023. Kulkarni AD et al: Fertility treatments and multiple births in the United States. N Engl J Med 369:2218, 2013. Mascarenhas MN et al. National, regional, and global trends in infertility prevalence since 1990: A systematic analysis of 277 health surveys. PLoS Med 9:e1001356, 2012. Slama R et al: Estimation of the frequency of involuntary infertility on a nation-wide basis. Hum Reprod 27:1489, 2012. Steiner AZ et al: Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. JAMA 318:1367, 2017. World Family Planning 2022. Available at https://www.un.org/ development/desa/pd/sites/www.un.org.development.desa.pd/files/ files/documents/2023/Feb/undesa_pd_2022_world-family-planning. pdf. Accessed November 22, 2023. World Health Organization: Infertility. Available at https://www. who.int/news-room/fact-sheets/detail/infertility. Accessed December 23, 2020. World Health Organization: WHO Laboratory Manual for the Examination and Processing of Human Semen. 6th ed. WHO Press; Geneva, Switzerland: 2021. Available at https://www.who.int/ publications/i/item/9789240030787. Accessed December 3, 2021.

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