Female Infertility

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Contents

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Key Points

- Female infertility is estimated to impact 1 in 7 couples in the Western world and is most often attributed to endometriosis, ovulatory disorders, and male factor infertility. Nearly 40% of female infertility cases are unexplained.
- The initial evaluation and examination of the infertile woman should include a comprehensive history, review of systems, physical examination, and, if required, laboratory testing and imaging to attempt to identify an underlying etiology or modifiable cause of infertility.
- Established treatment modalities are highly effective, and approximately 75% of infertile couples will achieve conception after evaluation and treatment.
- There are disparities in knowledge of, and access to, female infertility treatment. Special considerations should be made for patients who identify as LGBTQ+ and who desire biological children.

12.1 Introduction

Infertility is defined as the inability to establish a clinical pregnancy after 12 months of regular, unprotected sexual intercourse and is estimated to affect 1 in 7 couples in the Western world [1]. There are a host of factors that impact fertility and increasing recognition is being given to the impact of age; the current recommendation is that women over 35 seek an infertility evaluation after only 6 months. Endometriosis (30–50%), ovulatory disorders (21–25%), male factor (20%), tubal factors (14%), and uterine abnormalities (3.5%) are the leading, identifiable causes of female infertility (Fig. 12.1). Nearly 40% of female infertility cases are unexplained [2]. Infertility can be further classified as primary and secondary. Primary infertility is defined as women meeting the above criteria who have never been pregnant. Conversely, secondary infertility is the inability to become pregnant after a prior spontaneous pregnancy regardless of its outcome. Fortunately, an estimated 75% of infertile couples will achieve conception with individualized infertility evaluation and treatment [3].

Case Vignette

A 37-year-old woman attempting to conceive presents having had two prior pelvic infections with PID and an ectopic pregnancy for which the affected tube was removed. Her HSG imaging study shows a large hydrosalpinx in the remaining tube.

12.2 Diagnostic Criteria

As noted above, the inability to conceive after 1 year in women under age 35 or 6 months in women over age 35 is the working definition of infertility. There are many causes, with actual percentages ranging widely across different studies. The Centers for Disease Control and Prevention (CDC) cites age, smoking, excessive alcohol use, extreme weight fluctuations, and excessive physical or emotional stress as non-anatomical risk factors that increase the risk of female infertility [4].

12.3 Common Etiologies

12.3.1 Male Factor

A comprehensive analysis of the male partner's fertility should be performed in tandem with the female infertility evaluation. Semen analysis is the main screening tool for male infertility problems. Sperm function is not assessed in the semen analysis and, if indicated, should be evaluated by a reproductive urologist. Further information on the male infertility evaluation is discussed in ▶ Chap. 11.

12.3.2 Ovulatory Dysfunction

Ovulatory dysfunction will be identified in approximately 15% of all infertile couples and

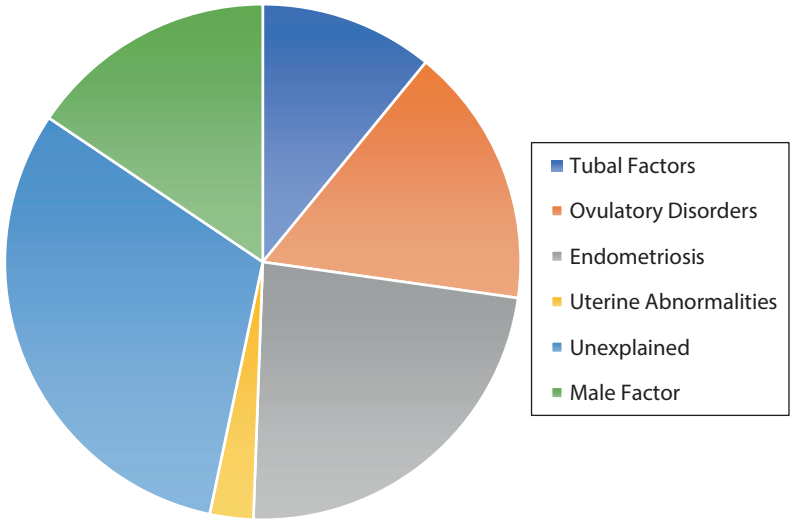

Fig. 12.1 Leading causes of female infertility

accounts for up to 40% of infertility in women. It can present as apparent menstrual disturbances including oligomenorrhea or amenorrhea but can also be more subtle. The underlying cause of dysfunction should be determined to allow for targeted treatment. Two of the most common etiologies of ovulatory dysfunction, polycystic ovarian syndrome (PCOS) and hyperprolactinemia, are described below [5].

12.3.2.1 Polycystic Ovarian Syndrome

PCOS is the most prevalent endocrine disorder in women, affecting 5–10% of the female population [6]. The Rotterdam Criteria, which replaced the National Institutes of Health (NIH) criteria, are used to define the PCOS diagnosis and incorporate the appearance of the ovaries on ultrasound into the diagnostic algorithm. The American Society of Reproductive Medicine (ASRM) diagnostic criteria require no other known endocrine abnormality and at least 2 of the following characteristics: (1) hyperandrogenism (e.g., hirsutism and oily skin), (2) irregular menses, or (3) polycystic ovaries [3]. These criteria are consistent with those published by the Androgen Excess and PCOS Society but differ in that the latter defines hyperandrogenemia and its associated clinical features as separate criteria [7]. Upon further testing, women may also show markedly elevated anti-Müllerian hormone (AMH) levels due to an increased number of small antral follicles and the intrinsic characteristics of their granulosa cells [1].

12.3.2.2 Hyperprolactinemia

In excess, prolactin, a hormone secreted by the anterior pituitary, suppresses secretion of gonadotropin releasing hormone (GnRH) from the hypothalamus, leading to reduced luteinizing hormone (LH) and resulting ovulatory dysfunction. Patients with a prolactinemia may present with galactorrhea, hypogonadism, and amenorrhea. Pituitary adenomas are the most common etiology of this clinical presentation, accounting for 7% of cases of female infertility. A prolactin level is indicated in the infertility evaluation in women with either irregular or absent cycles and/or symptoms such as galactorrhea.

12.3.3 Endometriosis

Endometriosis is a chronic gynecologic disorder in which endometrial tissue implants are outside the uterine cavity and is definitively diagnosed upon histological identification of endometrial glands and/or stroma outside the uterus in a sample of surgically removed tissue. The most commonly utilized classification system for endometriosis was developed

by the ASRM and utilizes anatomic location and severity of disease to define disease stages (I–IV) with potential etiologies including inflammation impairing ovarian function, pelvic adhesions or masses distorting pelvic anatomy, etc. [8]. The prevalence of endometriosis is considerably higher in sub-fertile women than in the general population, approximately 20–50% compared to 0.8–6% [9]. Importantly, the ASRM criteria do not correlate well with symptoms of pelvic pain or infertility and are not good predictors of pregnancy rates following treatment for endometriosis [10].

12.3.4 Pelvic and Tubal Adhesions

Pelvic and tubal adhesions are estimated to account for 12% of female infertility cases. These adhesions often develop secondary to infectious processes, most commonly pelvic inflammatory disease (PID) secondary to *Chlamydia trachomatis* infection, but may also form after pelvic surgery or due to endometriosis. Pregnancy rates are inversely proportional to the number of PID episodes and can be as low as 46% after three episodes of PID [8]. Pelvic adhesions increase the risk of a tubal (ectopic) pregnancy. Blocked tubes (hydrosalpinges) as well as pelvic adhesions can be treated surgically. However, pregnancy rates are still low and in vitro fertilization (IVF) is often the preferred route in these patients.

12.3.5 Systemic Diseases

The effects of various systemic diseases have been implicated in female infertility. Two common diseases with emerging evidence concerning infertility are described below.

12.3.5.1 Vitamin D Insufficiency

Vitamin D, a steroid hormone acquired through dietary intake or cutaneous exposure to UV light, has receptors in reproductive tissue. The physiologic implications of Vitamin D in female infertility are currently under exploration. It is postulated that the transcription of AMH, a key hormone for implantation, is dependent on vitamin D levels since the promoter region of the AMH gene contains a Vitamin D response element [11]. Studies have demonstrated that in women who are vitamin D replete, chances of achieving a positive pregnancy test, clinical pregnancy, and live birth after assisted reproductive technology (ART) are higher than those in women who are vitamin D deficient or insufficient [12, 13]. However, it is difficult to compare studies examining vitamin D levels and female infertility at large, as normal levels vary across institutions. Nonetheless, it is reasonable to prescribe vitamin D to women presenting for infertility evaluation, based on its beneficial risk-reward profile and lack of significant consequences noted to date [11].

12.3.5.2 Hypothyroidism (CH)

It is well established that hypothyroidism portends potential reproductive complications, including an increased incidence of infertility, miscarriage, and adverse obstetric and fetal outcomes [5]. However, the effect of subclinical hypothyroidism (SCH) – defined as a thyrotropin (TSH) level above the upper limit of normal but not in the abnormal range and normal free thyroxine levels (T4) – on female infertility remains in question, with or without the presence of anti-thyroid antibodies. The suggested prevalence of SCH in females of reproductive age is 3–8%. The strongest evidence to date suggests that SCH (TSH > 4 mIU/L) during pregnancy is associated with higher rates of miscarriage; however, a meta-analysis of levothyroxine (LT4) supplementation in infertile women with SCH found no significant association between LT4 supplementation and rates of clinical pregnancy, live birth, or preterm birth rates [14]. Given a lack of a single standard of care, alongside the low cost and safety of replacement, many practitioners will obtain patients' consent to offer treatment to achieve a TSH of <2.5.

12.4 Initial Evaluation of the Infertile Couple

The primary focus of the initial evaluation of the infertile couple is to identify potential etiologies and, ideally, modifiable factors that

may improve the chances of a couple establishing a successful pregnancy. The clinician should obtain a comprehensive history and perform a detailed physical examination. The initial evaluation appointment is also an opportunity for the care team to establish a sense of trust and collaboration with the couple given the stress and emotion that accompanies experiencing infertility.

12.4.1 History

The information gathered from a thorough medical history will enable the clinician to narrow down the wide range of potential etiologies and may permit a more targeted initial evaluation and treatment plan.

12.4.1.1 Demographics

The age of a female patient remains one of the most critical factors influencing her fertility. Data have suggested that fertility in women peaks in the early 20s and declines slowly until age 35 at which point this decline accelerates. For this reason, women older than 35 attempting to conceive are considered of late reproductive age.

12.4.1.2 Gynecological History

Menstrual history is a crucial aspect of a comprehensive gynecological history. An irregular menstrual pattern may suggest a thyroid, prolactin, or other hormonal etiology of the patient's infertility while symptoms such as dysmenorrhea and dyspareunia may provide useful information about risk factors for other conditions such as endometriosis. Furthermore, characteristics such as shortened cycles may be a potential indicator for diminished ovarian reserve. One important risk factor for early menopause is the patient's mother's age at time of menopause.

The following details should be included in the gynecologic history:

- Age of onset of menses
- Development of secondary sexual characteristics including breast (thelarche), pubic hair (pubarche), axillary hair, and the prepubertal growth spurt (adrenarche)
- Menstrual cycle characteristics including duration, flow, mid-cycle spotting, premenstrual symptoms, and changes from previous norm (including shortening of the normal cycle length)
- Symptoms of endometriosis such as dysmenorrhea and dyspareunia
- History of sexually transmitted diseases
- Previous methods of contraception and any complications
- Previous abnormal Pap smears and any associated interventions
- History of endometriosis, fibroids, ovarian cysts, and any associated interventions

12.4.1.3 Obstetrical History

If applicable, the following should be reviewed:

- Gravity, parity, pregnancy outcomes, and any associated complications
- Interval to conception with any previous pregnancy including whether fertility drugs or other interventions were used and whether the pregnancy was with the current partner

12.4.1.4 Medical History

The clinician should perform a thorough review of both the patient's and partner's past and present medical conditions including prior hospitalizations, medications, allergies, and history of communicable diseases. The preconception period is an ideal time to maximize the patient's health during pregnancy by optimizing any medical conditions such as diabetes, high blood pressure, or body mass index (BMI). Likewise, if the patient has a medical condition which is genetically transmitted, it is important to screen her partner and consider genetic counseling prior to attempts to conceive. There are a multitude of screening blood tests that cover a wide range of conditions and should be offered to all women considering pregnancy. Immunity status for rubella and varicella should be obtained and, if indicated, vaccination should be performed prior to conception.

12.4.1.5 Surgical History

Surgical procedures should be reviewed including gynecological or abdominal surgeries, for example, colorectal surgery for inflammatory bowel disease, which can lead to adhesive disease and affect fertility [15]. Additionally, information about minor, prior non-gynecologic surgeries, such as wisdom teeth removal, can be helpful as it provides information about the patient's response to anesthesia.

12.4.1.6 Family History

A thorough family history should be collected, specifically focusing on (1) history of subfertility in parents and siblings, (2) age of menopause in the patient's mother (as noted earlier, this is a risk factor for the proband) and, if surgically induced, the indication for surgery, and (3) heritable diseases including both medical conditions and birth defects. Historically, populations at risk for specific genetic diseases were screened upon initial evaluation at the recommendation of the American College of Obstetricians and Gynecologists [16]. Technology advancements now permit rapid testing for hundreds of disorders without regard for ethnicity or risk factors. This approach is performed by means of a simple blood or saliva test, which costs less than targeted testing and represents a comprehensive approach to identifying previously unscreened heritable conditions. Disadvantages of testing include the cost of generalized screening of all patients attempting to conceive, as well as the screen positive rate for non-actionable conditions, i.e., conditions that may not be clinically relevant. If a specific heritable condition is identified in the patient or their partner, screening for the condition should be discussed regardless of the clinical relevance to the patient's sub-fertility status. Similarly, for ethnicities with a higher prevalence of certain disorders (e.g., Ashkenazi Jewish ethnicity and Tay-Sachs disease), a special panel should be considered as indicated. Additional counseling may be provided by a genetic counselor, who can also aid in the determination of whom and how to screen. Patients who screen positive should be encouraged to share this information with family members in case they are carriers as well. If both patient and partner are carriers for the same condition, consideration should be given to IVF with genetic testing of the embryos, transferring only those embryos that will not result in an affected offspring.

12.4.1.7 Social History

Information regarding diet, exercise, environmental exposures, and substance use should be ascertained from all patients. Special attention should be paid to nutritional status, most importantly, adequate consumption of folic acid, calcium, and vitamin D. Folic acid intake is critically important to assess, given its known protective impact on certain birth defects; however, up to 30% of women attempting pregnancy may not be taking it, despite knowledge of its benefits [17]. The use of herbal preparations, vitamin supplements, or mega vitamins should also be ascertained, as they may contain hormones or anti-inflammatory agents that may impact fertility [18]. Exercise habits should also be reviewed since reproductive dysfunction has been reported to have a higher prevalence in athletes than in non-athletes. Environmental exposures at work or in the household should be addressed including smoking, exposure to second-hand smoke, alcohol consumption, and caffeine intake, as these have known effects on pregnancy success rates. Inhaled organic solvents (e.g., benzene, toluene) found in industrial compounds also impair female fertility; mechanistically, these molecules affect hormonal impairment, molecular alterations, oxidative stress, and DNA methylation [19].

12.4.1.8 Sexual History

To maximize the chance of conception, the clinician should discuss coital frequency and timing with the patient and their partner. Generally, intercourse is most likely to result in pregnancy when it occurs within the 3 days leading up to ovulation based on the survival time of sperm in the female reproductive tract [20, 21].

12.4.1.9 Considerations for LGBTQ+ Patients

Clinicians should be aware of special infertility considerations in the LGBTQ+ population. First, LGBTQ+ patients may be less likely to seek reproductive services due to a lack of culturally competent messaging. In the United States, the availability of electronic information regarding infertility treatment for LGBTQ+ patients varies by geographic region. Larger fertility clinics in the northeastern and western regions of the country are more likely to feature LGBTQ+ specific messaging, while those in the Midwest and South are significantly less likely to do so [22]. Second, special attention should be paid to fertility preservation in transgender individuals. Gender-affirming hormones may compromise gonadal function and lead to subfertility or infertility [23]. Thus, if conceiving biological children is a possible consideration for the patient, the clinician ought to refer them to a fertility specialist during initial discussions of gender-affirming treatment.

12.4.2 Review of Systems

In addition to the general medical history, a focused review of systems should be performed, targeting hormonal or physiologic abnormalities.

12.4.2.1 Headaches

Headaches are a common complaint in the outpatient setting and are benign in the majority of cases. However, headaches may reflect medical conditions and/or pituitary lesions which can negatively impact fertility [24–27]. The features of the patient's headache should be characterized; specifically, whether the pain is resolved with medication, presence of associated symptoms such as visual field disturbances, and whether the headaches are new or have changed in character. Additionally, patients should be counseled that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during ovulation or infertility treatment may adversely impact ovulation and subsequent implantation [28, 29].

12.4.2.2 Visual Changes

Visual impairment is a presenting feature of space-occupying pituitary lesions such as craniopharyngiomas or macroadenomas [30]. These pituitary lesions, if large enough, can extend out of the sella turcica and compress the optic chiasm. Although uncommon, this most frequently presents as bitemporal hemianopsia or bilateral loss of the peripheral visual fields. These patients often also simultaneously present to an infertility evaluation with menstrual dysfunction and/or galactorrhea.

12.4.2.3 Vital Signs and Physical Examination

Vital signs and a complete physical examination should be performed at the initial visit with emphasis on the following components.

Vital Signs

The vital signs assessment should focus on patient weight and BMI (discussed below), blood pressure, and pulse [31]. Hypertension may suggest an underlying disease known to affect female fertility, such as PCOS or endometriosis. Collecting a history of trends in the patient's blood pressure is also useful, as chronic hypertension can cause poor egg quality. Some medications used to treat female infertility may worsen or induce hypertension; therefore, patients should be advised of this risk before initiating treatment [32].

BMI

A BMI above or below the normal range has been associated with anovulation, oligoovulation, subfertility, and infertility [33]. Patients should be educated on the association between BMI and ovulation and counseled on lifestyle modifications to optimize their BMI. It is important to note that excessive weight negatively impacts fertility independent of ovulatory status. Furthermore, it is well accepted that obesity is associated with multiple high-risk obstetrical conditions such

as diabetes and hypertension that provide an independent incentive to lose weight.

Thyroid

Thyroid hormone disorders are associated with anovulation and menstrual irregularities. The thyroid gland is located in the anterior neck below the prominence of the thyroid cartilage and should be palpated for thyromegaly or nodules. Abnormalities on physical exam should be further evaluated with laboratory testing and possible imaging. In addition, any patient with menstrual cycle irregularities should have their TSH assessed.

Breast

The breast examination in the fertility evaluation should focus on symmetry of the breasts and any evidence of galactorrhea as this may be indicative of a pituitary lesion. Galactorrhea is defined as active secretion of breast milk at a physiologically inappropriate time, namely other than during pregnancy or lactation. Secretions are usually white in color and occur bilaterally from hormonal stimulation of multiple ducts. Conversely, pathological discharge usually originates from a single duct and is therefore unilateral and often nonwhite in color. One helpful technique is to have the patient squeeze her breast to attempt to express any discharge. She will likely provide more pressure than the provider and, in a patient who states that she has discharge, this will show what is necessary to generate the milk (i.e., gentle pressure or significant manipulation).

Abdomen

In cases of obesity, the abdomen should be evaluated for distribution of adipose tissue. Central adiposity in addition to other signs of hypercortisolemia could be associated with Cushing's syndrome. Additionally, the clinician should inspect thoroughly for any scars indicating previous surgery that the patient neglected to mention.

Skin

The skin should be evaluated for findings that can correlate with underlying endocrine pathology: acanthosis nigricans, abdominal striae, and hirsutism. Acanthosis nigricans is defined as hyperpigmented, velvety plaques found most commonly along the base of the neck, axilla, and the inner thighs. The formation of these lesions is thought to be triggered by hyperinsulinemia, a consequence of obesity-induced insulin resistance. Polycystic ovarian syndrome is often associated with insulin resistance; therefore, the presence of these lesions warrants further investigation.

Abdominal striae are characterized as violaceous striations most frequently noted on the skin of the abdomen and hips [34]. They can be associated with Cushing's syndrome and therefore warrant further evaluation for hypercortisolemia.

It is also important to assess the patient's hair growth pattern to assess for hirsutism. Hirsutism is the overgrowth of facial or body hair on women. Specifically, it can be seen as coarse, dark hair that may appear on the face, chest, lower abdomen, back, upper arms, or upper legs. Hirsutism is caused by hyperandrogenism, most commonly in the setting of polycystic ovarian syndrome, when the ovaries produce excessive amounts of androgens. Hirsutism can affect up to 10% of women and its presence should also help direct further laboratory testing [35]. In addition, the patient should be queried as to what she does for hair growth and maintenance to understand the severity and recognize that an absence of visible hair growth may reflect recent efforts on her part.

12.4.2.4 Gynecologic

The gynecologic exam should focus on identifying anatomical abnormalities that reflect congenital structural anomalies or organic diseases, both of which may impact fertility. For the purposes of the infertility evaluation, the gynecologic exam should assess for the presence of clitoromegaly and structural abnormalities of the cervix, uterus, and pelvis.

Normally, in the non-erect state, the clitoris is generally 3–4 mm in width, 4–5 mm in length and partially covered by a hood of skin. Clitoromegaly, enlargement of the clitoris, is a consequence of inappropriate androgen exposure and is typically defined as a size greater than 35 mm^2 [36]. This finding on

physical exam warrants further investigation about ingestion of exogenous androgens, possible in utero exposure to androgenic substances taken by the patient's mother, or an androgen-producing tumor. Physical signs of androgen excess should be correlated with laboratory testing.

Examination of the cervix should assess for cervical stenosis and structural abnormalities such as transverse ridges, cervical collars, hoods, coxcombs, pseudopolyps, cervical hypoplasia, and agenesis [37]. Cervical stenosis is the cervical abnormality most commonly associated with infertility. It decreases fertility by diminishing the mucus bridge from the vagina to the endocervix that is necessary for sperm transport. The remaining structural abnormalities are less common and can be secondary to idiopathic developmental anomalies or obstetrical trauma and surgical procedures. Exposure to diethylstilbestrol (DES), a synthetic estrogen, is historical and the associated anatomic findings are essentially no longer seen.

The bimanual examination should assess for cervical motion tenderness as well as structural abnormalities of the uterus and adnexae. Cervical motion tenderness can be elicited by gentle lateral movement of the cervix. This finding can be associated with an active or prior pelvic infection or adhesive disease. The mechanism of this physical exam finding is that the movement of the cervix causes movement of the adnexae as well. Therefore, in the setting of an infection or adhesions around or in the vicinity of the fallopian tubes or ovaries, sliding of the inflamed peritoneum with this test may elicit significant tenderness.

Even without pelvic adhesions, endometriosis can cause cervical motion tenderness when it involves structures attached to the cervix such as the vaginal apex, cardinal ligaments, uterosacral ligaments, or inferior aspect of the broad ligaments. The cervix may be laterally deviated as a result of ipsilateral shortening of a uterosacral ligament which has endometriosis, fibrosis, or a Müllerian anomaly such as a unicornuate uterus. Nodularity of the uterosacral ligaments can often be felt on bimanual examination if endometriosis is present in that region and may be especially prominent on recto-vaginal exam. The size and contour of the uterus should also be assessed on the bimanual exam. Notable findings such as enlargement, irregularity, asymmetry, or tenderness all warrant further investigation. Abnormalities associated with decreased fecundity include leiomyomata, adenomyosis, and Müllerian anomalies. The adnexae should also be evaluated on bimanual exam. Any abnormalities on bimanual pelvic examination should be further evaluated, typically with imaging such as ultrasound.

12.4.3 Diagnostic Testing

Following the medical history and physical exam, further testing is needed and can be divided into two categories: (1) preconception screening and (2) infertility evaluation.

12.4.3.1 Preconception Screening

Preconception screening consists of tests that should be performed on all women considering pregnancy. This includes a current Pap smear, type and screen, testing for sexually transmitted infections (STIs), and documentation of immunity to rubella and varicella. Recommended screening for STIs includes syphilis, hepatitis B surface antigen, HIV 1 and 2 antigen/antibody, hepatitis C antibody, and RNA-/DNA-based gonorrhea and chlamydia testing. Patients who are not immune to varicella or rubella should receive the appropriate vaccination at least 1 month prior to attempting conception. Women should also be up to date on their tetanus-diphtheria-pertussis vaccine [38]. When indicated, additional targeted well-women health screenings, such as mammograms, should be performed during this time to maximize health and avoid delays in screening tests.

12.4.3.2 Infertility Evaluation

The infertility evaluation consists of laboratory testing in addition to those performed for preconception screening. These tests assess ovulatory function and ovarian reserve. Imaging studies such as hysterosalpingography and sonohysterography are also typically performed, and if warranted from the patient's

history or physical exam, hysteroscopy or laparoscopy may be indicated as well.

Thyroid-Stimulating Hormone (TSH)

Hypothyroidism is a relatively common medical problem in women and can result in ovulatory dysfunction even in the presence of minimal or no symptoms. Fortunately, it is relatively easy to treat. TSH is the screening test of choice for identifying thyroid hormone abnormalities and should be performed at the initial infertility visit. Hypothyroidism is suggested when TSH is elevated and should be repeated with a measurement of free T4 [39]. When TSH is abnormally low, it can indicate hyperthyroidism and further testing is required. As previously mentioned, there remains controversy surrounding the clinical significance of subclinical hypothyroidism (SCH) in women attempting to conceive. Given a lack of a single standard of care, alongside the low cost and safety of replacement, some practitioners will obtain patients' consent to offer treatment to achieve a TSH of <2.5.

Prolactin

Hyperprolactinemia is an important cause of oligomenorrhea or amenorrhea. The most common cause for hyperprolactinemia in women is a prolactin-secreting adenoma usually diagnosed with MRI after an elevated prolactin is identified on bloodwork and confirmed on repeat sampling. It is also important to note that thyrotropin-releasing hormone (TRH) is a potent prolactin stimulating substance and since this is increased along with TSH in hypothyroid states, prolactin levels can be elevated in women with hypothyroidism [40]. For this reason, TSH and prolactin should be drawn together at the initial evaluation in women with menstrual irregularities as appropriate to establish the correct diagnosis. Lastly, a careful medication history should be taken as various medications can also contribute to an elevated prolactin.

Ovulatory Function

Ovulatory function can often be deduced from a patient's menstrual history. Women with regular cycles (25–35 day intervals) and symptoms such as breast tenderness, bloating, and dysmenorrhea are likely to have normal ovulatory function. As previously noted, several hormonal abnormalities can commonly cause ovulatory dysfunction in otherwise healthy patients.

Therefore, tests such as TSH and prolactin are important to obtain in tandem in women with irregular cycles. Other tests such as midluteal serum progesterone and urine luteinizing hormone surge detection can provide additional information about ovulatory function. The infertility evaluation and treatment have evolved such that if a woman presents with regular cycles many practitioners will not assess for ovulatory dysfunction given a low yield, alongside the use of fertility drugs such as clomiphene citrate which may correct any subtle disturbances.

▪ Serum Progesterone

Measurement of serum progesterone levels can also be used to document ovulation. Serum progesterone levels below 2–3 ng/mL are consistent with no ovulation when measured at the appropriate time. After ovulation, progesterone is secreted from the corpus luteum and levels rise steadily until they peak approximately 7–8 days following ovulation. Typically, a serum progesterone level > 3 ng/mL provides reliable evidence that ovulation has taken place but does not provide information on when it occurred [41]. Serum progesterone levels are not typically used to assess the strength or adequacy of ovulation but rather whether the patient has or has not ovulated. A serum progesterone may be valuable if the plan is to induce menstruation via a course of exogenous progesterone (e.g., medroxyprogesterone acetate) followed by a withdrawal bleed. If only a pregnancy test is obtained prior to administering medroxyprogesterone acetate, it is possible that the patient may be in her luteal phase and/or with an early pregnancy.

▪ Basal Body Temperature Charts (BBTs)

Progesterone is a thermogenic hormone and will slightly raise core body temperature. Women can measure their temperature with a

thermometer designed to show smaller differences in temperature. This can show ovulation and duration of the luteal phase based on endogenous progesterone production. Taking one's temperature every day can be stressful, and as the temperature only rises after ovulation, these are typically not recommended especially given the utility of urine LH detection kits.

▪ Urinary Luteinizing Hormone (LH)

Of the tests described in this section, measurement of urinary LH is the only test that can predict ovulation before it occurs, thereby giving patients the ability to time intercourse to attempt conception. These highly accurate over-the-counter tests are designed to change color when urinary LH levels reach those associated with the mid-cycle LH surge, indicating imminent ovulation. Testing should be performed daily starting 3 days before the expected day of ovulation to ensure that ovulation is not missed. Ovulation will generally follow within 12–36 hours following a positive surge with the variability reflecting the once daily testing of an ongoing process. If used for timed intercourse or intrauterine insemination (IUI) , the day after the first positive test will have the highest success rate of clinical pregnancy [42].

12.4.3.3 Ovarian Reserve Testing

Ovarian reserve has become an integral part of the infertility evaluation and can be assessed with several methods. It is well known that fertility declines with a woman's age due to the decrease in oocyte quantity and quality. The tests most commonly used to assess ovarian reserve include early follicular phase follicle-stimulating hormone (FSH) and estradiol levels, anti-Müllerian hormone (AMH), and antral follicle count (AFC). Other tests, such as the clomiphene citrate challenge test (CCCT), are employed infrequently.

▪ FSH and Estradiol

FSH is a hormone secreted by the pituitary gland and functions to recruit follicular cohorts. As ovarian reserve diminishes, the pituitary gland increases FSH production in order to compensate. It has been shown that when baseline FSH levels are >10 IU/L, success with therapies including IVF is diminished [43]. Estradiol levels should be drawn with all basal FSH levels to demonstrate that a low FSH level is not falsely suppressed secondary to a prematurely elevated estradiol level (defined as greater than 60–80 pg/mL). Although a day 3 FSH was required historically, FSH and estradiol levels can be drawn on either cycle day 2 or 3 to facilitate the process for the patient [44].

▪ Anti-Müllerian Hormone (AMH)

Anti-Müllerian hormone, also known as Müllerian inhibiting substance (MIS), is produced by the granulosa cells of ovarian follicles and reflects the primordial follicle reserve. Unlike other ovarian reserve tests, AMH can be measured at any point during the menstrual cycle. Levels less than 1.0 ng/mL are considered abnormal and are associated with poor ovarian response to gonadotropin stimulation [45, 46].

▪ Antral Follicle Count (AFC)

The AFC is determined using transvaginal ultrasound in the early follicular phase to quantify the number of follicles between 2 and 10 mm in diameter. These antral follicles may be thought of as eggs in the "pipeline" reflecting overall ovarian reserve and can be used as a predictive measure of overall future production. An AFC of less than 10 has been shown to correlate with poor ovarian response to gonadotropin stimulation [47]. High antral follicle counts are often associated with PCOS.

▪ Clomiphene Citrate Challenge Test (CCCT)

Clomiphene citrate is a selective estrogen receptor modulator (SERM) that has an antagonist effect on the hypothalamus, therefore blocking the inhibitory feedback of estrogen. This in turn leads to an increase in GnRH and therefore FSH at the level of the pituitary. The CCCT is a provocative examination designed to "unmask" those patients with a normal day 3 FSH level. With this test, a basal FSH level and estradiol are measured on cycle day 3. The patient is given clomiphene citrate 100 mg daily on cycle days 5 through 9 and the FSH level is again measured on cycle day

10. The test is considered abnormal if the day 3 FSH, day 3 estradiol, or day 10 FSH levels are elevated [48]. Given the utility of tests for AMH and AFC, and the fact that the CCCT requires exogenous medication (clomiphene citrate) and a second blood draw on day 10, this test is obtained infrequently.

12.4.4 Imaging Studies

12.4.4.1 Ultrasonography

Transvaginal ultrasonography is the first-line imaging study for identifying structural abnormalities in the pelvis, particularly of the uterus and ovaries [49]. It should be considered if a structural lesion is suspected on physical examination. In addition, the ultrasound probe can be used to push on structures to localize symptoms (such as pain in an endometrioma) as well as to assess sliding of the ovary or uterus alongside bowel to assess for adhesions. However, some conditions may be undetectable, especially if the exam is limited by patient discomfort, body habitus, or if any abnormalities are located above the field of view. Transvaginal ultrasound may be considered in all infertile women, especially if the plan is to obtain an AFC.

12.4.4.2 Sonohysterography

Sonohysterography (also known as saline infusion sonography or SIS) is an imaging test that utilizes transvaginal ultrasonography in which a fluid medium, typically saline, is instilled through the cervix to distend the uterine cavity in the early follicular phase after the conclusion of menses. More accurate than transvaginal ultrasound alone, this increases the provider's ability to identify endometrial or intracavitary lesions such as polyps or fibroids and intrauterine adhesions (synechia). When used with specialized contrast media (saline with bubbles infused), sonohysterography may also be used to attempt to assess tubal patency. If combined with 3D ultrasound, SIS provides significant information about the uterus including possible differentiation of uterine anomalies such as a bicornuate from a septate uterus.

12.4.4.3 Hysterosalpingography

Hysterosalpingography (HSG) is a radiographic evaluation of the uterine cavity and fallopian tubes. Contrast dye is injected through the cervix into the uterine cavity with spillage of the dye into the abdominal cavity if the fallopian tube(s) are patent. This test is used to diagnose synechia and other intracavitary defects such as polyps and fibroids as well as Müllerian anomalies such as a septate or bicornuate uterus. Furthermore, hysterosalpingography can not only assess tubal patency but also potentially identify the site of obstruction if the fallopian tubes are blocked. Of note, although the primary purpose of this study is not therapeutic, oil-based media have been shown to increase subsequent pregnancy rates [50]. The HSG is not as sensitive as the SIS for evaluating the cavity; however, because it provides greater details about the tubes, it is often the first-line test in an infertility evaluation.

12.4.5 Surgery

Hysteroscopy involves introducing a small diameter telescope with a light source through the cervix into the uterine cavity. Similar to sonohysterography, saline is typically used to distend the cavity. Hysteroscopy is often considered the gold standard for visualizing the cavity and can be used for both diagnostic and therapeutic purposes. Diagnostic hysteroscopy can often be performed in the office when there is suspicion for an intracavitary lesion based on the patient's history such as abnormal uterine bleeding or specific findings noted on prior imaging. Hysteroscopy in the office provides the advantage of potentially being able to immediately treat any findings found (i.e., "see and treat") if the lesions are small. For more substantial findings (i.e., fibroids), anesthesia is typically required; hence, the study is more commonly performed in the operating room.

Laparoscopy can be useful for some infertile women since it is the only definitive method of accurately diagnosing anatomic lesions such as endometriosis and intraperitoneal adhesions and the only modality to treat

structural findings. However, as fertility treatments have evolved, fewer laparoscopies are done for infertility alone, as IVF provides higher pregnancy rates with a lower risk of ectopic pregnancy in women with pelvic pathology. Furthermore, laparoscopic treatment of low-stage endometriosis results in only a small absolute increase in pregnancy rates, requiring many women to undergo a laparoscopy to achieve a pregnancy [51].

Nevertheless, in situations where higher stage endometriosis or pelvic pathology is suspected, the patient has significant pelvic pain which she desires to be addressed surgically, or IVF is not able to be performed, then laparoscopy may be an excellent option for both diagnostic and therapeutic purposes.

12.5 Treatment

There are many options for infertility treatment. Specific therapies should be selected based on the results of the patient's evaluation as described above. As many of these therapies can be extremely expensive and are not necessarily covered by medical insurance, it is always ideal to begin with the least invasive and least expensive option. However, there has been greater movement to move immediately to IVF if pregnancy has not been achieved with lesser treatment [52]. Furthermore, some conditions such as tubal blockage and severe male factor dictate moving directly to IVF.

12.5.1 Oral Medications

Clomiphene citrate is a selective estrogen receptor modulator (SERM) that inhibits the negative feedback effect of estrogen on the hypothalamus and, therefore, upregulates the hypothalamic–pituitary–gonadal axis to increase the likelihood of ovulation in anovulatory women or the release of more than one egg in women who are already ovulatory. Letrozole functions as an aromatase inhibitor, decreasing the peripheral enzymatic conversion of androgens to estrogens. This overall decreases the body's estrogen level and provides feedback to the hypothalamic–pituitary–gonadal axis to similarly increase FSH production.

When using these medications, it is important to distinguish patients who have ovulatory infertility from those with unexplained and ovulatory infertility. In women who are anovulatory, the goal is to achieve monofollicular development. Letrozole has emerged as a superior choice over clomiphene in this population [53].

In women who are ovulatory and not conceiving despite releasing an egg each month, the goal is to increase their ovulatory function using a more aggressive protocol. Clomiphene citrate remains the protocol of choice over letrozole [53].

As opposed to the traditional 50 mg during cycle days 5–9, the standard dosing regimen for clomiphene, when used for ovulation induction, is 100 mg orally during cycle days 3–7. Furthermore, to optimize pregnancy rates, this should be combined with intrauterine insemination (IUI) as ovulatory women who take clomiphene and utilize timed intercourse do not have an increased pregnancy rate compared to non-medicated cycles [54].

12.5.2 Ovarian Stimulation (Injectable Gonadotropins)

Controlled ovarian stimulation with gonadotropins (i.e., follicle stimulating hormone) is used to stimulate the ovaries to produce one egg in anovulatory women refractory to oral medications and more than one mature follicle per cycle in women who are infertile and not conceiving. Multiple follicular development increases both the chances of any one egg fertilizing (and therefore overall pregnancy rates) and also more than one egg fertilizing (increasing the risk of multiple gestations). Gonadotropin therapy is more effective than clomiphene or letrozole for ovulatory women with infertility [55]. Side effects of these medications include ovarian hyperstimulation syndrome (OHSS) and ovarian damage or torsion.

Multiple gestations typically only occur in 1–2% of naturally occurring pregnancies. With injectable gonadotropins, 20–30% of

these pregnancies are associated with multiple implantations. Multiple pregnancies are associated with an increased risk of miscarriage, preterm delivery, pregnancy-induced hypertension, postpartum hemorrhage, and other maternal complications. Given the accepted goal of avoiding multiple gestations, especially high-order multiple gestations, many providers avoid using gonadotropins other than with IVF, especially as the literature supports a faster time to pregnancy by moving directly from clomiphene to IVF [52].

12.5.3 Intrauterine Insemination

Intrauterine insemination (IUI) is a procedure performed in the ambulatory setting in which prepared sperm is placed directly into the woman's uterus through a catheter. When treating ovulatory infertile women, IUIs are typically included routinely in the treatment regimen to maximize pregnancy rates.

There are several indications for IUI alone including the use of donor sperm, male factor infertility such as low motility [56], coital dysfunction, cervical factor such as no mucous production, or stenosis due to a surgical procedure such as a loop electrosurgical excision procedure (LEEP) or cone biopsy. IUIs will not be effective in patients with tubal blockage, severe endometriosis, or intraabdominal adhesions since they still require the oocyte to travel from the ovary to the uterine cavity. IUI alone is not indicated for ovulatory women with unexplained infertility or in medicated cycles in anovulatory women.

12.5.4 Assisted Reproductive Technology

Assisted reproductive technology (ART) consists of technologies in which eggs or embryos are handled which narrows the definition to IVF. If only the sperm is handled (e.g., intrauterine insemination), this is not considered ART by the CDC [57]. IVF is the most successful fertility intervention in any one treatment cycle for the majority of women. It involves ovarian stimulation with injectable gonadotropins typically with the use of a gonadotropin-releasing hormone (GnRH) agonist or a GnRH antagonist to suppress the LH surge and premature ovulation. Human chorionic gonadotropin (hCG) is typically given to mature the eggs, triggering ovulation. The oocytes are then retrieved through needle aspiration transvaginally under ultrasound guidance. In some cycles, all oocytes and/or embryos may be frozen, for example, when the indication is fertility preservation or when genetic testing (e.g., preimplantation genetic testing) is done. Alternatively, the oocytes can be fertilized with a prepared sperm sample and incubated. The embryos are graded using quality assessment criteria such as cell regularity, degree of fragmentation, and other microscopic characteristics [58]. Those of highest quality are selected for transfer, which is performed transcervically through a small catheter under ultrasound guidance. Supplemental progesterone is used to support the luteal phase since no ovulation takes place in IVF, and there may be inadequate endogenous progesterone production.

The live birth rate using IVF varies widely depending on many factors including, but not limited to, the woman's age, BMI, duration of infertility, and presence of hydrosalpinges. Importantly, of these, the woman's age is perhaps the most important and the factor used when quoting pregnancy rates. The goal of IVF is to achieve a singleton pregnancy, given the risks associated with twins or higher order multiple gestations. The Society for Assisted Reproductive Technology has an excellent website with information about IVF and pregnancy rates [59], as well as a calculator to help predict pregnancy rates [60].

12.5.5 Donor Gametes

Donor gametes (sperm or eggs) or donor embryos should be discussed with appropriate patients. Care should be taken to anticipate and prepare for the period of grieving or anger associated with these routes in patients

who have not anticipated this need. Patients should be given time and resources to address the psychological aspects of the situation prior to pursuing either of these options and psychological counseling is recommended [61]. Of note, although specific recommendations are made for counseling when donor gametes are used, psychological support should be available for all patients presenting with infertility given the associated stress.

12.5.6 Adoption, Fostering, and Childfree Living

While advances in female infertility evaluation and treatment have greatly improved the rate of successful pregnancies, a percentage of couples will fail all interventions and/or be unwilling or unable to continue treatment. If these couples are unwilling to consider adoption, the clinician should be prepared to discuss childfree living, a concept that may be difficult for infertile couples to accept. It is important to recognize that couples may perceive childfree living as their personal failure and are prone to develop depressive symptoms or even marital conflict as a result [62]. Fortunately, there is evidence to suggest that cognitive-behavioral therapy focused on validating emotion, educating on the psychological effects of infertility and treatment, and providing tools to manage emotions can significantly reduce couples' rejection of the childfree lifestyle [63]. During this grieving period, clinicians may refer patients for support to reduce couples' psychological and relational burdens.

12.6 Comparison of International Protocols for Evaluation of Female Infertility

Country of Origin	United States	Canada	United Kingdom	Germany, Switzerland, and Austria
Publishing Body	American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice	Canadian Fertility and Andrology Society	National Institute for Health and Care Excellence (UK)	German Society of Gynecology and Obstetrics; Swiss Society of Gynecology and Obstetrics; Austrian Society of Gynecology and Obstetrics
Last Updated	2019	2002	2017	2020
Definition of Infertility	Failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse	Inability to conceive after 1 year of unprotected intercourse	The period of time people have been trying to conceive without success after which formal investigation is justified and possible treatment implemented	Failure to achieve a successful pregnancy after 12 months or more of appropriate, timed, unprotected intercourse

Country of Origin	United States	Canada	United Kingdom	Germany, Switzerland, and Austria
Recommendations on Etiology Testing	*Serum TSH:* Perform for women with ovulatory dysfunction, infertility, or evidence of thyroid disease *Serum Prolactin:* Perform in women with irregular menses or signs of hyperprolactinemia *Tubal Patency:* Evaluate using hysterosalpingography and/or hysterosalpingo-contrast sonography *Sexually Transmitted Infections:* Obtain exposure information during initial medical interview *Endometrial Biopsy:* Perform only when endometrial pathology (e.g., neoplasia, chronic endometriosis) is strongly suspected	*Serum TSH:* Do not measure in the absence of irregular cycles *Serum Prolactin:* Do not measure in the absence of irregular cycles *Tubal Patency:* Evaluate using hysterosalpingogram *Sexually Transmitted Infections:* Perform endocervical culture to rule out asymptomatic disease prior to performing uterine instrumentation *Endometrial Biopsy:* Do not perform	*Serum TSH:* Offer only to women with symptoms of thyroid disease *Serum Prolactin:* Offer only to women who have an ovulatory disorder, galactorrhea, or a pituitary tumor *Tubal Patency:* Offer hysterosalpingogram to women with no known uterine comorbidities to rule out tubal occlusion *Sexually Transmitted Infections:* Offer screening for *CChlamydia trachomatis* prior to performing uterine instrumentation *Endometrial Biopsy:* Do not offer to evaluate the luteal phase	*Serum TSH:* Perform for all women; if greater than 2.5 mU/L, measure anti-thyroid antibody level *Serum Prolactin:* Perform at time of diagnostic workup *Tubal Patency:* Evaluate using laparoscopy with chromopertubation or hysterosalpingo-contrast sonography (HyCoSy) *Sexually Transmitted Infections:* Not stated *Endometrial Biopsy:* Do not perform if menstrual cycle length is unremarkable and regular
Evaluation of Ovarian Reserve	*Antral Follicle Count:* Perform for evaluation of etiology of infertility	*Antral Follicle Count:* Not stated	*Antral Follicle Count:* Perform as an initial predictor of success through natural conception or with IVF	*Antral Follicle Count:* Perform during diagnostic workup for hormonal disorders
Recommendations on Lifestyle Factors	*Obesity:* Obtain BMI during initial physical examination *Low Body Weight:* Obtain BMI during initial physical examination *Smoking:* Obtain history during initial medical interview	*Obesity:* Recommend a supervised weight-loss program regardless of ovulatory status *Low Body Weight*: Not stated *Smoking:* Advise to give-up smoking	*Obesity:* Advise women with a BMI $\geq$ 30 to lose bodyweight *Low Body Weight:* Advise women with a BMI < 19 to increase body weight *Smoking:* Offer a referral to a smoking cessation program	*Obesity:* Advise women with a BMI of > 30 to lose weight *Low Body Weight:* Advise women with a BMI < 19 and disordered ovulation to increase body weight *Smoking:* Discuss potential negative impact during initial medical interview

12.7 Concluding Remarks

Although infertility is a relatively common medical problem, the process of evaluation and treatment can be long, emotionally taxing, and frustrating. Patients should be encouraged to seek care in a timely fashion with a provider who can attempt to expedite their treatment using modern techniques. The role of the provider is to offer support while maintaining realistic expectations based on the clinical evidence at hand. As in other fields of healthcare, there are disparities in access to, and awareness of, infertility treatment. Black women present later for infertility treatment and are less likely to pursue treatment than white women [64]. Providers for women of minority populations should establish open communication lines to encourage patients to seek treatment if they so choose. While there are many options for infertility treatment at this time, a relatively large proportion of infertility does not carry a readily obtainable diagnosis. Therefore, further research is required to better understand how and why infertility occurs, as well as to develop innovative treatment techniques and optimize existing ones. Fortunately, current technologies allow a majority of patients to achieve their dream of a family.

12.8 Review Questions

1. A 28-year-old woman with no significant past medical history presents to an outpatient OB/GYN clinic. She reports an inability to conceive despite regular, timed intercourse for the past 4 months. She has no family history of subfertility. She is concerned and requests to begin an infertility evaluation. As her provider, which of the following is the most appropriate response?
   A. The patient meets diagnostic criteria. Initiate a formal infertility evaluation.
   B. The patient does not yet meet diagnostic criteria. Advise her to continue her practices and return at 6 months. If she has not conceived by then, she will meet criteria for infertility evaluation.
   C. The patient does not yet meet diagnostic criteria. Question her further on her family history, as a family history of subfertility is a diagnostic criterion.
   D. The patient does not yet meet diagnostic criteria. Advise her to continue her practices and return at 1 year. If she has not conceived by then, she will meet criteria for infertility evaluation.

2. A 23-year-old transgender man presents to clinic for consultation on gender-affirming surgery. During your medical interview, you discover the patient desires to start a biological family in the future. How can you honor their request?
   A. Advise the patient that unfortunately conceiving a biological child will not be possible if they desire gender-affirming surgery.
   B. Refer the patient to a fertility specialist to discuss options for preserving fertility after gender-affirming procedures have been initiated.
   C. Refer the patient to a fertility specialist to discuss options for preserving fertility before gender-affirming procedures have been initiated.
   D. Forgo referral to a fertility specialist and refer the patient to an adoption counselor.

3. A 37-year-old woman attempting to conceive presents having had two prior pelvic infections with PID and an ectopic pregnancy for which the affected tube was removed. Her HSG imaging study shows a large hydrosalpinx in remaining tube. Based on current evidence, you tell her:
   A. Her best chance for pregnancy is surgery to repair the remaining tube.
   B. Her best chance for pregnancy is in vitro fertilization.

C. Her best chance for pregnancy is clomiphene citrate with intrauterine inseminations (IUI).
D. She will not be able to conceive and should consider adoption.

12.9 Answers

1. D

2. C

3. B

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