Treatment of infertility in women
Carriann Smith, Maureen Grimm, and Megan Schwegel

Objective: To review causes and risk factors associated with infertility, relevant diagnostic procedures, and available pharmacologic and nonpharmacologic treatment options; to identify common dosing, administration, adverse effects, and key counseling points associated with infertility treatments; and to describe the role of the pharmacist in caring for patients with infertility.

Data sources: Available clinical literature identified through searches of Medline and review of major textbooks in reproductive medicine.

Study selection: Studies were selected primarily to reflect current infertility treatment practices in the United States. The specific criteria evaluated included date of the study, date of publication, study population, including diagnosis, baseline characteristics, and nationality; and number of participants.

Data synthesis: Treatment of infertility often involves the use of both pharmacologic and nonpharmacologic therapy. This article provides an overview of these pharmacologic treatments and provides two tables that outline the key administration and safety concerns with these products. Nonpharmacologic procedures associated with diagnosis and treatment also are outlined.

Conclusion: Pharmacists are an excellent resource for patients suffering from infertility. First, pharmacists answer questions about administration and safety of these medications. Second, pharmacists discuss available treatment options and assist with referrals to specialists as needed. Third, pharmacists can provide emotional support for patients who may otherwise suffer in silence.

Keywords: Infertility, pregnancy, reproduction, women’s health, pharmacy services.

Abstract

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Reviews

Learning objectives
At the conclusion of this knowledge-based activity, the pharmacist will be able to:

- Recognize the causes and risk factors associated with infertility.
- Describe the different diagnostic approaches used to determine infertility.
- Compare the available pharmacologic and nonpharmacologic treatment options for all the causes of infertility.
- Identify common dosing, administration, adverse effects, and key counseling points associated with infertility treatments.
- Explain the role of the pharmacist in the treatment as well as the emotional component of infertility.

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Carriann Smith, PharmD, is Associate Professor of Pharmacy Practice and Director of Outreach, College of Pharmacy and Health Sciences, Butler University, Indianapolis, IN. Maureen Grimm, PharmD, is a PGY-1 community practice resident, College of Pharmacy, University of Georgia, Athens, and College of Pharmacy and Health Sciences, Butler University, Indianapolis, IN. Megan Schwegel is a student pharmacist, College of Pharmacy and Health Sciences, Butler University, Indianapolis, IN.

Correspondence: Carriann Smith, PharmD, College of Pharmacy and Health Sciences, Butler University, 4600 Sunset Ave., Indianapolis, IN 46208. Fax: 317-940-6172. E-mail: crichey@butler.edu

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Role of the pharmacist
As infertility treatment continues to improve in the United States, more couples are seeking medical care for infertility, including pharmacotherapy treatments. According to the 2002 National Survey of Family Growth, 12% (7.3 million) of reproductive-aged women (15–44 years) in the United States reported use of infertility services.1,2 The websites of the Centers for Disease Control and Prevention and American Pregnancy Association indicate that approximately 6 million women aged 15 to 44 years have difficulty getting or staying pregnant.3,4

Because age is an important risk factor for infertility, the criteria for an infertility diagnosis depends on the age of the patient. For women aged 35 years or older, infertility is diagnosed when pregnancy has not occurred within 6 months of frequent, unprotected intercourse. For women younger than 35 years, 1 year of frequent, unprotected intercourse without pregnancy is considered to indicate infertility. Patients who meet this definition of infertility should consult a physician, although most patients delay seeking treatment until they have not become pregnant for 2 years or more.5

As the use of infertility medications increases, pharmacists need to provide patients with accurate information. Pharmacists can assist patients by discussing their individual situations in a supportive atmosphere. To do so, pharmacists must be educated on the causes, risk factors, and treatment options for infertility.

Active learning exercise: List two conditions/abnormalities among female patients that may cause infertility.

Etiology
Infertility may be related to factors in the man, woman, or both. The two major causes of female infertility are ovulatory dysfunction (20%–40%) and tubal and pelvic (including cervical) pathology (30%–40%). Some experts separate cervical and pelvic pathology from tubal pathology. Because the treatment courses are similar for tubal, pelvic, and cervical causes of infertility, the authors chose to group these together in Figure 1. Categorization of these diagnoses and reported prevalence ranges vary. This should not be surprising because treatment plans are highly individualized by patient; laboratory ranges are only a guide, and patients may have multiple factors. The prevalence ranges provided herein are adapted from multiple sources but most closely resemble those reported by Fritz and Speroff5 and other sources.6,7

Ovulation disorders include oligoovulation (infrequent ovulation) or anovulation (absence of ovulation). When women fail to ovulate regularly, fewer oocytes are available for fertilization. The World Health Organization lists the following three classifications for ovulatory disorders, and hyperprolactinemic anovulation is considered a fourth category8:

- WHO group I: Hypogonadotropic hypogonadal anovulation represents 5% to 10% of anovulatory women with low serum estradiol levels and low to low-normal serum follicle-stimulating hormone (FSH) levels. These women have an abnormal response or a decreased production of gonadotropin-releasing hormone (GnRH).
- WHO group II: Eugonadotropic estrogenic anovulation represents 75% to 85% of anovulatory women with normal estradiol and FSH levels. Patients with polycystic ovary syndrome (PCOS) belong to this category.
- WHO group III: Hypergonadotropic anovulation represents 10% to 20% of anovulatory women and includes those with elevated serum FSH levels. Many of these women have amenorrhea resulting from premature ovarian failure. Women who have diminished ovarian reserve because of advanced age are managed similarly to those with premature ovarian failure.
- Hyperprolactinemic Anovulation represents 5% to 10% of anovulatory women who do not ovulate as a result of hyperprolactinemia or thyroid disorders. Laboratory results may be similar to patients with hypogonadotropic hypogonadal anovulation.

The primarily cause of tubal damage is pelvic inflammatory disease secondary to chlamydia or gonorrhea. Other causes of tubal damage are peritoneal or pelvic disorders, including endometriosis, adhesions from previous surgeries, appendicitis, inflammatory bowel disease, and pelvic tuberculosis. Laparoscopy allows the practitioner to evaluate the damage to assist with determining the cause. The aforementioned conditions cause pelvic inflammation, and this impairs movement of both the oocyte and sperm through the fallopian tube. Tubal damage also involves unexplained factors such as the possibility of congenital anomalies. In addition to tubal damage, endometriosis can cause other disruptions to the female reproductive system, including pelvic adhesions, direct damage to ovarian tissue secondary to the growth and/or removal of excess endometrial tissue, and production of substances that impair normal hormone function.

Other causes (10%–20%) of infertility include unresolved male factor infertility and chromosomal abnormalities. A discussion of other causes of infertility could include a variety of rare conditions, as well as drug-induced infertility caused by cancer chemotherapy. We have chosen to highlight conditions such as uterine abnormalities, unresolved male factor, chromosomal abnormalities, and unexplained infertility. Uterine and chromosomal abnormalities may cause early miscarriage that is interpreted
as infertility. In a study published in 2005, infertile couples were found to have more chromosomal rearrangements than the general population.8 If male factor infertility is not resolved, female patients will usually undergo in vitro fertilization (IVF) treatment including intracytoplasmic sperm injection (ICSI). A diagnosis of unexplained infertility suggests normal ovulatory function, a normal uterine cavity, and bilateral tubal patency.

**Risk factors**

In a study conducted in the United Kingdom, increased female age was found to be the single most important risk factor in cases of unexplained infertility.9 The study of 7,172 infertile couples who attended the Aberdeen Fertility Centre in Scotland from 1993 to 2006 found that 26.6% of older women (35–39 years) were diagnosed with unexplained infertility compared with 21% of younger women (<30 years). Various statistical analyses showed a significant association between female age and diagnosis of female infertility. The diagnosis of unexplained infertility was more common in women older than 35 years. Tobacco use has been associated with infertility.10,11 Most studies evaluating the association between tobacco use and fertility have examined the effect of the amount of cigarettes smoked per day on fertility. Decreased rates of conception occur mostly in women who smoke more than 10 cigarettes per day. In a study of 108 patients having IVF, active smoking induced significantly more oxidative stress and could explain the impaired ability to form ova. This increased oxidative stress can lead to DNA damage, and cigarette smoke causes premature aging of the ovaries, in turn decreasing female fertility.

Some researchers suggest that alcohol use is linked with infertility; however, this association remains contradictory.10 Studies have reported that moderate to heavy female drinkers take longer to conceive. Other studies reported no adverse effect on ovulation or association with infertility in women who consumed varying amounts of alcohol.

Caffeine is another dietary factor that shows inconsistent effects on infertility.10,12 Studies linking caffeine use with infertility generally found the effect in those consuming 300 to 500 mg caffeine per day. Caffeine may increase estrogen production or decrease estrogen metabolism. A comprehensive review of human studies of caffeine and reproductive health by Peck et al.12 indicated that the weight of evidence does not support a positive relationship between caffeine consumption and infertility in women.12 A patient’s weight can also affect infertility.13 Both underweight and overweight women are at increased risk of infertility, with effects found with body mass indexes (BMIs) of less than 17 or greater than 27 kg/m², respectively. The decreased fertility found with increased BMI is associated with insulin resistance. Excess insulin can result in an androgen excess, leading to altered ovarian physiology and a possible decreased ovulation.14 Decreased BMI specifically resulting from decreased caloric intake or increased exercise has been correlated with anovulation. This is thought to be a result of a decrease in GnRH, which leads to a decrease in FSH and luteinizing hormone (LH), potentially in-
increasing the risk for infertility. Studies comparing infertility rates and aerobic exercise have found that increased aerobic exercise (>7 hours vigorous exercise/week) has the ability to contribute to increased infertility in women as a result of decreased FSH and LH levels leading to anovulation.15

Pharmacists should be aware of these risk factors and prepared to discuss them with patients. Determining the patients’ existing risk factor awareness and readiness for change will keep the lines of communication open, especially when addressing lifestyle changes such as weight loss.

**Diagnostic information**

Identifying the underlying cause for an infertility diagnosis is an important step toward treatment. This provides the practitioner with the information necessary to establish an individual treatment plan. Considering the importance of increased female age as a risk factor in infertility, assessing ovarian reserve is fundamental to determining whether an aggressive treatment plan is needed. The single most important test for assessing ovarian reserve is anti-Müllerian hormone.5 Other hormones associated with assessing ovulatory disorders include progesterone, estradiol, FSH, and inhibin B. Table 1 describes these and other laboratory tests used to diagnose the cause of infertility.16,17 Office procedures or outpatient surgery may be used to assess ovulatory disorders but are most useful in assessing tubal, pelvic, and uterine abnormalities.

**Active learning exercise:** Identify one laboratory test and one radiologic test that are frequently used to assess fertility.

These procedures include but are not limited to hysterosalpingography, hysteroscopy, transvaginal ultrasound, saline infusion sonohysterography, and laparoscopy.

**Hysterosalpingography (HSG)** is a radiologic assessment of uterine cavity and fallopian tubal patency performed by injection of contrast dye through the cervical canal to allow visualization of width of the cervical canal, contour of the uterine cavity, outline of the lumen of fallopian tubes, presence or absence of spillage of contrast from the fimbriated ends of the tubules, and outline of peritoneal structures. This allows the physician to detect fallopian tube damage or cervical/uterine structural abnormalities and endometrial polyps, if present.18,19 HSG is the most frequently used radiologic procedure associated with assessment of fertility. HSG has little risk to the patient. Infection, iodine reaction, and fainting have occasionally been reported, and patients should report any fever, abdominal pain, and/or any lightheadedness following the test.

**Hysteroscopy** is a procedure that inserts a hysteroscope into the uterus to allow visualization of the endometrial cavity, including the tubal ostia, endocervical canal, cervix, and vagina. The physician is able to evaluate the presence of lesions in the endometrial cavity and may rule out uterine/cervical pathology. Of important note, this procedure is not sufficient for evaluating fallopian tubal damage and usually requires further testing to diagnose the cause of infertility.18,20 Hysteroscopy also has little risk. Rarely, patients may experience injury to endometrial cavity, infection, heavy bleeding, or adverse effects from the anesthesia. Slight cramping or bleeding for 1 to 2 days is possible.

Transvaginal ultrasound involves inserting a sound wave–generating probe into the vagina. These waves are reflected off of body structures and passed to a computer, which creates images. The probe is moved to allow visualization of pelvic organs. This procedure allows the physician to detect abnormalities of the ovaries, uterus, vagina, and other pelvic structures and may help to identify pelvic inflammatory disease.18,20 No known risks are associated with administering transvaginal ultrasounds.

**Saline infusion sonohysterography** is a procedure in which saline is infused into the uterine cavity to enhance endometrial visualization during transvaginal ultrasound. Saline solution may help outline abnormal masses. Although, this procedure improves the physicians’ ability to detect polyps, malignancy, adhesions, and hyperplasia, it is not used alone for the diagnosis of infertility.20 No known risks exist for this procedure, although patients may experience cramping after the procedure as a result of the infusion of saline into the uterine cavity.

**Laparoscopy** is a procedure performed in the hospital or outpatient surgery center under general anesthesia that allows the physician to directly visualize the contents of the pelvis. A small incision is made below the patient’s umbilicus and a needle is inserted. Carbon dioxide gas is passed into the abdomen to allow for a bigger space so that the physician can see the area clearly. A laparoscope (small camera) is placed through the incision to enable the physician to see the inside of the patient’s pelvis and abdomen. Dye may or may not be injected to enable clearer visualization of the fallopian tubes. This allows the physician to visualize pelvic abnormalities that may lead to infertility such as endometriosis and peritubular adhesions. Therefore, laparoscopy is commonly used in women with pelvic/peritoneal abnormalities, unexplained infertility, and/or multiple risk factors for infertility before treatment is initiated.18 Laparoscopy is associated with general surgery risks. Patients should rest and limit work for 2 to 3 days following the procedure. The gas used to inflate the abdomen may cause shoulder pain after the procedure, and this pain can be treated with prescription or over-the-counter pain relievers.

**Treatment**

Many treatment options are available for patients with infertility. Pharmacotherapy may be used alone or in conjunction with assisted reproductive technologies. With an increase in the number of patients seeking treatment, treatment commonalities exist for groups of patients based on etiology. Sample treatment progressions are outlined in Figure 1. An individual’s treatment plan may be established based on factors such as diagnosis, prioritization when multiple diagnoses are present, physician practice characteristics, provider experience, patient risk factors, length of time couple has been trying, patient specific religious, and social and economic factors.

Clinicians may define efficacy of pharmacologic treatments for infertility as producing the necessary effect, such as inducing ovulation. Patients, however, may consider the ultimate measure of efficacy to be successful live birth. Researchers may argue, however, that additional factors, such as the quality of prenatal care, weak-
en the link between successful infertility treatment and live birth. A middle ground would be the number of successful pregnancies. Regardless of the measurement desired, data linking individual pharmacotherapy options with specific efficacy are insufficient. Other than initial treatment with clomiphene citrate or aromatase inhibitors, rarely is a single pharmacologic treatment used without other interventions or therapies.

General and obstetrics/gynecology practitioners may feel comfortable ordering an initial fertility assessment and prescribing oral agents. If these efforts are unsuccessful, patients should seek the assistance of a reproductive endocrinologist. Pharmacists have roles in supporting general practitioners and patients and in making suggestions for referral. The Society for Assisted Reproductive Technology (SART) provides data on its website documenting overall IVF success rates for SART member clinics and the results for specific clinics. The rapidly changing knowledge base and technical skills needed for these complex treatment regimens are best managed by reproductive endocrinologists.

At this time, most pharmacists will not be involved in selecting therapeutic agents for infertility according to efficacy. Tables 2 and 3 outline key features associated with these pharmacologic treatments to support pharmacist interactions with patients. Pharmacists should be aware of the different treatment options in order to answer questions about dosing, administration, and safety. Pharmacists may also discuss with patients the availability of different treatments and ways to reduce risk factors. Pharmacists who are aware of local clinic specifics can provide appropriate referrals for patients. Many patients may think that IVF is the only option for an infertility diagnosis.

Community pharmacists should be aware that pharmacy computer systems may guide pharmacists to make confusing counseling statements. This is because pharmacy computer systems may advise patients to not take these agents while pregnant. Careful consideration is needed to appropriately counsel patients receiving infertility treatment. Nonpharmacologic procedures are mentioned within the discussion of pharmacotherapy and are further defined in the following section. These procedures include intrauterine insemination (IUI), IVF, ICSI, and donor eggs.

Pharmacists should be aware that treatments are intended to produce changes that are likely to cause normal or exaggerated hormonal responses and subsequent undesirable reactions. These reactions may be classified as adverse events but relate more to hormonal changes than the medications themselves. The information provided in Tables 2 and 3 are derived from careful review of information and references provided in three primary databases:

Table 1. Laboratory tests used to diagnose the cause of infertility

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Description</th>
<th>How performed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal body temperature</td>
<td>Used to detect time of ovulation; test is inexpensive but difficult to interpret. Potential benefit in diagnosing and treating female infertility, although clinical utility is limited.</td>
<td>Measure temperature under the tongue with basal body thermometer every morning before getting out of bed, using the bathroom or eating/drinking anything.</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Used to assess ovulation function. Low progesterone level indicates decreased or absent ovulation.</td>
<td>Serum test collected mid–luteal phase 1 week before expected menses.</td>
</tr>
<tr>
<td>Anti-Müllerian hormone</td>
<td>Used to assess ovarian function; it is able to reliably detect declining ovarian function early. Reflects the number of follicles, although no established threshold value. (Most insurers do not cover this test.)</td>
<td>Measured at any time during the menstrual cycle.</td>
</tr>
<tr>
<td>Estradiol</td>
<td>Used to evaluate ovarian cyst or ovarian reserves. Higher levels may indicate a functional ovarian cyst or decreased ovarian reserve.</td>
<td>Measured on day 3 of menstrual cycle (day 1 being first day of full menses).</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone (TSH)</td>
<td>Used to assess hypothyroidism (which can affect fertility). Elevated TSH plus low/normal T4 (free thyroxine) indicates hypothyroidism.</td>
<td>Measured on day 3 of menstrual cycle (day 1 being first day of full menses).</td>
</tr>
<tr>
<td>Follicle-stimulating hormone</td>
<td>Used to evaluate presence ovarian follicles and oocytes.</td>
<td>Measured on day 3 of menstrual cycle (day 1 being first day of full menses).</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Used to assess ovulation. High levels of prolactin may interfere with ovulation.</td>
<td>Measured on day 3 of menstrual cycle (day 1 being first day of full menses).</td>
</tr>
<tr>
<td>Inhibin B</td>
<td>Used to evaluate reduced follicles and oocytes. Test is not widely available outside of research laboratories. Low inhibin B levels indicate decreased ovarian reserves.</td>
<td>Measured on day 3 of menstrual cycle (day 1 being first day of full menses).</td>
</tr>
</tbody>
</table>

![Figure 2. Normal female reproductive cycle](http://commons.wikimedia.org/wiki/File:MenstrualCycle2_en.svg)
Table 2. Use, dosing, and administration of infertility medications

<table>
<thead>
<tr>
<th>Medication category, hormone (brand name—manufacturer)</th>
<th>Medication use</th>
<th>Route of administration and dose</th>
<th>Administration considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective estrogen receptor modulator, clomiphene citrate (Clomid—Sanofi-Aventis and Serophene—EMD Serono)</td>
<td>Treatment of ovulatory disorders</td>
<td>25–100 mg p.o. for 5 days. Not recommended for more than six cycles or doses &gt;150 mg.</td>
<td>Orally administered at same time each day. Complete fertility evaluation should be completed before initiation of therapy.</td>
</tr>
<tr>
<td>Aromatase inhibitors, letrozole (Femara—Novartis), anastrozole (Arimidex—AstraZeneca)</td>
<td>Off-label treatment of ovulatory disorders and ovulation induction.</td>
<td>Letrozole: 2.5 mg p.o. daily starting on day 3 of menses and continued for 5 days. Can be done for three cycles. Anastrozole: 1 mg p.o. daily starting on day 3 of menses and continued for 5 days. Can be done for three cycles.</td>
<td>Orally administered; taken without regard to meals.</td>
</tr>
<tr>
<td>Gonadotropin-releasing hormone (GnRH) agonist, leuprolide for subcutaneous injection (Lupron—Abbott), leuprolide for subcutaneous injection (Lupron—TAP), leuprolide for subcutaneous injection (Gonal-f—EMD Serono)</td>
<td>Depot form approved for the use in endometriosis: temporarily shrinks endometrial lesions. Unapproved use with controlled ovarian hyperstimulation: used to down regulate before initiating gonadotropins.</td>
<td>For endometriosis: 3.75 mg i.m. every month or 11.25 mg i.m. once every 3 months for a maximum of 6 months. For infertility: dose varies; subcutaneous administration.</td>
<td>Intramuscular depot should be administered in physician office. Store unopened vials in refrigerator. Vials in use can be kept at room temperature for several months with minimal loss of potency.</td>
</tr>
<tr>
<td>GnRH agonist, goserelin (Zoladex—AstraZeneca), nafarelin (Synarel—Pfizer)</td>
<td>Endometriosis: to temporarily shrink the endometrial lesions</td>
<td>Goserelin: 3.6 mg s.c. pellet every 28 days. Nafarelin: nasal spray: one spray in one nostril in morning and other nostril in evening.</td>
<td>Goserelin: store at room temperature, protect from light, and dispense in light-safe bag. Nafarelin: do not use topical nasal decongestants for at least 2 hours after nafarelin use. Avoid sneezing immediately after use.</td>
</tr>
<tr>
<td>Gonadotropin/follitropin, follitropin alfa (Gonal-f—EMD Serono), follitropin beta (Follistim—Organon)</td>
<td>Treatment of ovulatory disorders in women</td>
<td>Subcutaneous injection various dosages depending on cycle and used alone or with assisted reproductive technology</td>
<td>Follicin beta may be administered subcutaneously or intramuscularly. Follitropin alfa is available as powder for solution and follitropin beta as pen cartridge or powder for solution. Powder can be room temperature or refrigerated. Solution must be refrigerated after opening and should be used within 28 days. Protect from light. Assist patients with injection technique. When reconstituting powder, avoid shaking. Resulting solution should be clear.</td>
</tr>
<tr>
<td>Gonadotropin/follitropin, Urofollitropin (Bravelle—Ferring)</td>
<td>Treatment of ovulatory disorders</td>
<td>Subcutaneous or intramuscular injection following by HCG. Instruct patient on injection technique.</td>
<td>Subcutaneous or intramuscular injection followed by HCG. Instruct patient on injection technique.</td>
</tr>
<tr>
<td>Gonadotropin/luteinizing hormone, lutropin alfa (Luveris—EMD Serono)</td>
<td>Hypogonadotropic hypogonadism</td>
<td>75 IU daily until adequate follicular development is noted; maximum duration of treatment: 14 days. Should be administered with follicin.</td>
<td>Solution should be clear and colorless. Any unused portion after reconstitution should be discarded. Instruct patient on injection technique. Administer around naval area.</td>
</tr>
<tr>
<td>Gonadotropin/menotropins (Menopur—Ferring and Repronex—Ferring)</td>
<td>Stimulate the development of multiple follicles, ovarian induction.</td>
<td>Repronex: subcutaneous or intramuscular. Menopur: subcutaneous various dosages depending on specific cycle.</td>
<td>Any unused reconstituted material should be discarded. The lower abdomen (alternating sides) should be used. Solution should be clear and free from particulate matter before administering.</td>
</tr>
<tr>
<td>Ovulation triggers, human chorionic gonadotropin (HCG) (Novarel—Ferring and Pregnyl—Organon), Recombinant HCG (Ovidrel—EMD Serono)</td>
<td>Ovulation triggers</td>
<td>HCG: 5,000–10,000 units i.m. 1 day after last dose of menotropin. Recombinant HCG: 250 mcg prefilled syringe given subcutaneously as one dose the day after finishing follicle-stimulating hormone.</td>
<td>Instruct patient on administration technique. Patients should be instructed to administer HCG injection at the specific time indicated by the reproductive endocrinologist.</td>
</tr>
<tr>
<td>GnRH antagonists, cetrorelix (Cetrotide—EMD Serono), ganirelix</td>
<td>Suppress luteinizing hormone production at the pituitary level.</td>
<td>Cetrorelix or ganirelix 0.25 mg/day can be administered during early to late follicular phase until HCG administration. Cetrorelix 3 mg given as a one time dose on any day during days 5–9.</td>
<td>Use subcutaneously only. Cetrorelix should be reconstituted. Ganirelix provided as prefilled syrings should only be used once.</td>
</tr>
</tbody>
</table>
Clinical Pharmacology, Lexi-Comp, and Facts and Comparisons 4.0. When using tertiary databases to access information about adverse events for infertility patients, pharmacists must carefully consider the primary source of the information.

Figure 2 provides an overview of the normal female menstrual cycle. The figure shows the changes in pituitary hormones (referred to as gonadotropins in the current work), ovarian hormone levels, and changes to the uterine lining, cervical mucus, and basal body temperature. Several of the diagnostic tests outlined in Table 1 corresponded to expected changes in hormone levels during the normal cycle.

### Pharmacotherapy treatment options

#### Ovarian hyperstimulation

Several medications can be used to induce ovulation in women suffering from ovulatory disorders. These medications may also be used in controlled ovarian hyperstimulation (COH) in patients without documented ovulatory disorders to improve the number of available oocytes for assisted reproductive technologies such as IUI or IVF. Additional oocytes will improve a patient’s chances of achieving a pregnancy. COH involves inducing an exaggerated hormonal response to cause the maturation of multiple oocytes.

#### Clomiphene citrate

Clomiphene citrate (Clomid—Sanofi or Serophene—EMD Serano) is approved by the Food and Drug Administration (FDA) for treating ovulatory dysfunction in female patients suffering from infertility. As a nonsteroidal selective estrogen receptor modulator, clomiphene citrate blocks and down regulates estrogen receptors. This results in elevated levels of FSH and LH. This stimulates follicular growth and leads to ovulation without directly stimulating the ovary. Women with normal FSH levels and who produce adequate estrogen are most likely to benefit from clomiphene citrate. Several studies have investigated the use of clomiphene in other populations. Some studies have specifically shown that patients with PCOS may also benefit from initial treatment with clomiphene citrate. Clomiphene citrate is often used as a first-line and last-resort agent because it is the cheapest treatment. It is not recommended to be used for more than six cycles. Pharmacists may need to counsel patients with tubal or pelvic abnormalities who are repeatedly using this product to avoid more costly therapies. Pharmacists may also assist patients by referring them to a reproductive endocrinologist. Vasomotor symptoms are the most commonly seen adverse event, occurring in 10% or more of patients. Ovarian enlargement is also common and should be monitored for resolution. Less than 10% of patients are likely to experience adverse effects such as abdominal discomfort, breast discomfort, and nausea. Less than 2% of patients may experience visual changes such as blurred vision, flashes, or spots. If visual changes occur, the patient’s physician should be contacted and the medication discontinued. As with most fertility treatments, there is a risk for multiple births. Patients who respond inadequately to clomiphene citrate may find a need for supplemental therapy to enhance their response. These other options include dexamethasone, human chorionic gonadotropin (HCG), metformin, thiazolidinediones, and gonadotropins. The use of adjunct therapy is more common in patients with PCOS.

#### Aromatase inhibitors: Letrozole and anastrozole

Aromatase inhibitors are increasingly being used for patients with ovulatory disorders. Letrozole (Femara—Novartis) and anastrozole (Arimidex—AstraZeneca) may be used in patients with normal or elevated estrogen concentrations, irregular ovulation, or PCOS. Letrozole and anastrozole are nonsteroidal competitive

<table>
<thead>
<tr>
<th>Table 2 continued</th>
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<tbody>
<tr>
<td>Insulin sensitizers, metformin (Glucophage—Bristol-Myers Squibb)</td>
</tr>
<tr>
<td>Micronized progesterone, oral capsule 100 or 200 mg (Prometrium—Catalent; Abbott), vaginal gel 4% or 8% (Crinone—Watson), oil for injection, vaginal insert (Edometrin—Ferring), suppository compounding kit (CurtisPharma)</td>
</tr>
<tr>
<td>Dopamine agonist, bromocriptine (Parlodel—Novartis), cabergoline</td>
</tr>
<tr>
<td>Antplatelet, aspirin</td>
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Abbreviation used: FDA, Food and Drug Administration; IU, International units; PCOS, polycystic ovary syndrome.
### Table 3. Safety and counseling points for infertility medications

<table>
<thead>
<tr>
<th>Medication category, hormone, brand name (manufacturer)</th>
<th>Contraindications/special considerations</th>
<th>Major drug interactions</th>
<th>Key patient counseling points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective estrogen receptor modulator, clomiphene citrate (Clomid—Sanofi-Aventis and Serono), letrozole (Femara—Serono), anastrozole (Arimidex—AstraZeneca)</td>
<td>None known</td>
<td>May trigger symptoms similar to menopause. Ovulation is expected 5–10 days after last dose. Complete pregnancy test before repeat courses. Avoid driving a car or operating machinery until patients know how the medication will affect them. Vaginal dryness is possible and may be bothersome to patients attempting frequent intercourse.</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin releasing hormone (GnRH) agonist, leuprolide (Lupron—Abbott), nafarelin (Synarel—AstraZeneca)</td>
<td>Contraindicated during pregnancy (Category X)</td>
<td>May diminish effects of antidepressants agents.</td>
<td>Patients using depot for endometriosis should also use nonhormonal birth control. Monitor bone mineral density in patient using intramuscular treatment for endometriosis. Case reports of anaphylactic reactions. Note that higher doses are reserved for other indications.</td>
</tr>
<tr>
<td>GnRH agonist, goserelin, (Zoladex—AstraZeneca), nafarelin (Synarel—Pfizer)</td>
<td>Pregnancy Category X</td>
<td>May diminish effects of antidepressants agents.</td>
<td>Monitor bone mineral density. Patients with diabetes patients should monitor blood glucose carefully. Adverse effects may improve over time. Vaginal bleeding/spotting may persist after 2 months of treatment. Adherence to schedule is very important.</td>
</tr>
<tr>
<td>Gonadotropin/follitropin, follitropin alfa (Gonal-f—EMD Serono), follitropin beta (Follistim—Organon)</td>
<td>None known</td>
<td>High risk of multiple gestation and OHSS. Patients should be instructed not to miss appointments or laboratory tests.</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin/follitropin, urfollitropin (Bravelle—Ferring)</td>
<td>None known</td>
<td>High risk of multiple gestation and OHSS. Educate patients on observation and management of mild allergic reaction. Assist patients with injection technique. When reconstituting powder, avoid shaking. Do not use if reconstituted solution is not clear. Use immediately after reconstitution.</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin, luteinizing hormone, lutropin alfa (Luveris—MD Serono)</td>
<td>None known</td>
<td>Assist patients with injection technique. When reconstituting powder, avoid shaking. Do not use if reconstituted solution is not clear. Use immediately after reconstitution.</td>
<td></td>
</tr>
<tr>
<td>Gonadotropin/ menotropins, (Menopur—Ferring and Repromex—Ferring)</td>
<td>None known</td>
<td>High risk of multiple gestation and OHSS. Educate patient on proper technique and placement of injections. Powder may be stored at room temperature or refrigerated. Protect from light. After reconstitution, inject immediately and discard unused portion.</td>
<td></td>
</tr>
</tbody>
</table>

**Adverse effects**
- Flushing, headache, diaphoresis, gastrointestinal disorders
- Ovarian enlargement, headache, hot flashes, breast discomfort, abdominal discomfort/bloating, nausea and vomiting, visual disturbances, multiple gestations
- Contraindicated in pregnancy (Category X). Liver enzyme abnormalities with continued use. No dose adjustment for mild to moderate hepatic function; no studies in severe hepatic insufficiency.
- Ovarian cyst, abdominal cramps, OHSS, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, ovarian cyst, abdominal cramps, OHSS, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, fatigue, nausea, diarrhea, constipation, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, abdominal pain, abdominal cramps, injection site reactions, bloating, nausea and vomiting, pain, dizziness, tachycardia, OHSS, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins

**Contraindications**
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X

**Major drug interactions**
- Use immediately after reconstitution.
- Use immediately after reconstitution.
- Use immediately after reconstitution.
- Use immediately after reconstitution.
- Use immediately after reconstitution.

**Key patient counseling points**
- None known
- None known
- None known
- None known
- None known
- None known

**Safety and counseling points for infertility medications**
- Headache, abdominal pain, abdominal cramps, injection site reactions, bloating, nausea and vomiting, pain, dizziness, tachycardia, OHSS, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Ovarian enlargement, headache, hot flashes, breast discomfort, abdominal discomfort/bloating, nausea and vomiting, visual disturbances, multiple gestations
- Contraindicated in pregnancy (Category X). Liver enzyme abnormalities with continued use. No dose adjustment for mild to moderate hepatic function; no studies in severe hepatic insufficiency.
- Ovarian cyst, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, ovarian cyst, abdominal cramps, OHSS, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, fatigue, nausea, diarrhea, constipation, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, abdominal pain, abdominal cramps, injection site reactions, bloating, nausea and vomiting, pain, dizziness, tachycardia, OHSS, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins

**Common conditions recorded in patients on gonadotropins**
- OHSS, rare thromboembolic and/or pulmonary conditions
- Headache, emotional liability
- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins

**Common adverse effects**
- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
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**Safety and counseling points**
- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins
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- Headache, abdominal pain, vaginal bleeding, depression, weight gain, OHSS, emotional liability, injection site reactions, rare thromboembolic and/pulmonary conditions recorded in patients on gonadotropins

**Injectable preparations**
- Leuprolide acetate (Lupron—Abbott)
- Nafarelin (Synarel—AstraZeneca)
- Goserelin (Zoladex—AstraZeneca)
- Intramuscular treatment for endometriosis.

**Antidiabetes agents**
- May diminish effects of antidiabetes agents.
- Patients using depot for endometriosis should also use nonhormonal birth control. Monitor bone mineral density in patient using intramuscular treatment for endometriosis. Case reports of anaphylactic reactions. Note that higher doses are reserved for other indications.

**Additional considerations**
- None known
- None known
- None known
- None known
- None known
- None known

**Pregnancy Category X**
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X
- Pregnancy Category X

**Interactions**
- May diminish effects of antidiabetes agents.
- Patients using depot for endometriosis should also use nonhormonal birth control. Monitor bone mineral density in patient using intramuscular treatment for endometriosis. Case reports of anaphylactic reactions. Note that higher doses are reserved for other indications.

**Injection technique**
- Assist patients with injection technique.
- When reconstituting powder, avoid shaking.

**Pregnancy test**
- Complete pregnancy test before reconstitution.

**Ovulation**
- Ovulation is expected 5–10 days after last dose.
Unlike clomiphene citrate, these agents do not block estrogen receptors. This eliminates the negative impact on the endometrium. This class is not FDA approved for these indications. The primary concern regarding use of these agents is that they are classified in Pregnancy Category X, with a risk of possible congenital anomalies. A careful review of the adverse event profile suggests that short-term use (i.e., 5 days) is not long enough to induce noteworthy adverse events.

### Table 3 continued

<table>
<thead>
<tr>
<th>Ovulation triggers, human chorionic gonadotropin (HCG; Novarel—Ferring and Pregnyl—Organon), recombinant HCG (Ovidrel—EMD Serono)</th>
<th>Edema, injection site pain, thromboembolic disorder, headache, irritability</th>
<th>Some formulations may contain benzyl alcohol and should be avoided in patients with hypersensitivity. Contraindicated after conception (Pregnancy Category X). Safety has not been established in patients with hepatic or renal insufficiency.</th>
<th>None known</th>
<th>Ovulation occurs approximately 36 hours after first injection. Hormones will circulate in blood for days after injection—may result in a false-positive pregnancy test. Ovidrel is prefilled syringe. Inject into stomach area. Store Ovidrel in refrigerator and protect from light. Following reconstitution of others, solutions are stable for 30–60 days, depending on the specific preparation. Keep all physician appointments and specific time schedule.</th>
</tr>
</thead>
<tbody>
<tr>
<td>GnRH antagonists, cetorelix (Cetrotide—EMD Serono), ganirelix</td>
<td>Abdominal pain, hot flashes, headache, vaginal bleeding or menstrual irregularity, injection site reactions, nausea and vomiting, hepatic impairment</td>
<td>Ganirelix syringe contains natural rubber and could cause a reaction in patients with latex allergy, Pregnancy Category X.</td>
<td>None known</td>
<td>Instruct on injection technique. Patient must follow specific timing provided by prescriber. Patient must keep all laboratory and prescriber appointments. Use immediately after mixing.</td>
</tr>
<tr>
<td>Insulin sensitizers, metformin (Glucophage—Bristol-Myers Squibb)</td>
<td>Diarrhea, nausea and vomiting, flatulence, headache, indigestion, hypoglycemia, vitamin B12 deficiency, weight loss, lactic acidosis</td>
<td>Avoided in patients with hepatic and renal disease. Avoid/limit alcohol (increased risk of lactic acidosis)</td>
<td>Counsel on symptoms of hypoglycemia and how to deal with a hypoglycemic attack. Monitor for hematologic parameters and renal function. Check vitamin B12 and folate if anemia is present. Take with food to decrease gastrointestinal upset. Take at same time every day. Lactic acidosis is rare but potentially severe consequence of therapy.</td>
<td></td>
</tr>
<tr>
<td>Progesterone, oral capsule 100 or 200 mg (Prometrium—Catalent; Abbott), vaginal gel 4% or 8% (Crinone—Watson), oil for injection, vaginal insert (Edometrin—Ferring), compounding kit (CurtisPharma)</td>
<td>Dizziness, abdominal pain/cramping, headache, nausea, mood swings, irritability/depression, fatigue, breast tenderness, diarrhoea/constipation, disorientation, fluid retention</td>
<td>No studies on use in hepatic and renal insufficiency. Contains peanut oil and should not be used by patients with peanut allergy.</td>
<td>Rivaroxaban, silodosin, and topotecan. St. John’s wort may decrease progestosterone levels. Avoid activities that require mental alertness until patients know whether it will affect them. Discuss peanut allergy/warning with capsules and gel. Avoid using other vaginal drugs 6 hours before or after. If pregnancy occurs, may continue until placenta autonomy. Prepare patients for vaginal discharge for vaginally administered medications.</td>
<td></td>
</tr>
<tr>
<td>Dopamine agonist, bromocriptine (Parlodel—Novartis)</td>
<td>Nausea, headache, dizziness, fatigue, lightheadedness, vomiting, abdominal cramps, constipation/diarrhoea, muscle weakness, rinitis, drowsiness/somnolence</td>
<td>The effect of renal and hepatic impairment has not been evaluated. Caution should be used during pregnancy and postpartum and risks and benefits should be considered. Use cautiously in patients who are at risk of cardiovascular events or psychosis.</td>
<td>Major substrate of CYP3A4, ergot alkaloids, alpha/beta agonists, anti-psychotics, conivaptan, cyclosporine, dasatinib, efavirenz, itraconazole, macrolide antibiotics, MAO inhibitors, methylphenidate metoclopramide, nitroglycerin, posaconazole, protease inhibitors, serotonin 5-HT1 receptor agonists, serotonin modulators, tocilizumab, voriconazole</td>
<td>When taken with ethanol, an increase in gastrointestinal adverse effects or ethanol intolerance may occur. Take at the same time each day. Maintain adequate hydration. Discuss risks and benefits with patients when used during pregnancy or postpartum.</td>
</tr>
<tr>
<td>Antiplatelet, aspirin</td>
<td>Indigestion, nausea and vomiting, bleeding not common with low dose but serious</td>
<td>Anticoagulants, other antiplatelets, clot busters</td>
<td>May have benefit during first and second trimesters, but studies have not shown a definite advantage.</td>
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</tbody>
</table>

Abbreviations used: CYP, cytochrome P450; ECG, electrocardiogram; HT, hydroxytryptamine; MAO, monoamine oxidase; OHSS, ovarian hyperstimulation syndrome.
Comparison of clomiphene citrate versus aromatase inhibitors. Casper\textsuperscript{25} reviewed two studies demonstrating the efficacy of letrozole in women with PCOS. His conclusion was that letrozole is at least as effective as clomiphene citrate for inducing ovulation and achieving pregnancy in patients with PCOS. Letrozole is likely to produce less adverse effects and may require less monitoring than clomiphene citrate.

Badawy et al.\textsuperscript{26} evaluated pregnancy outcomes after the use of aromatase inhibitors or clomiphene citrate for unexplained infertility. Patients were randomized to three groups: anastrozole 1 mg daily for 5 days, 5 mg letrozole daily for 5 days, or 100 mg clomiphene citrate daily for 5 days. A control group of 200 women were matched by age to women who conceived naturally during the same 3.5 years of the trial. Clinical pregnancy occurred in 36 (11.1\%) patients receiving letrozole, 15 (10.5\%) receiving anastrozole, and 77 (12.1\%) receiving clomiphene citrate compared with 21 (7.0\%) patients in the control group. Deliveries occurred in 30 (83\%) patients receiving letrozole, 11 (73\%) receiving anastrozole, and 65 (78\%) receiving clomiphene citrate. Clomiphene citrate showed the highest pregnancy rate, although the difference was not statistically significant. Letrozole was associated with a higher delivery rate but was also not statistically significant.

Regarding fetal safety, two infants born from the letrozole group had congenital anomalies and one had early neonatal death. No other groups reported early neonatal death, but one infant in the clomiphene citrate group had a congenital anomaly. Early reports suggest an increase of congenital cardiac and bone malformations in newborns of mothers using letrozole. In 2008, Elizur and Tulandi\textsuperscript{27} evaluated the literature to assess the fetal safety of drugs used for infertility. The results suggested that after several cycles of clomiphene citrate, a slightly higher risk of neural tube defects and severe hypospadias is possible. A review of aromatase inhibitors shows flawed studies, and the use of aromatase inhibitors with other agents makes it difficult to draw conclusions. Two small studies referenced in the review indicated that the miscarriage rate and teratogenicity were not different for clomiphene citrate and aromatase inhibitors and that miscarriage and teratogenicity were generally unfounded for both treatments. Additional data are needed to confirm or refute the rare possibility of congenital anomalies with the use of clomiphene citrate and aromatase inhibitors in infertility.\textsuperscript{27}

In conclusion, data are not sufficient to support a clear recommendation of clomiphene citrate or aromatase inhibitors in all infertility patients. Additional studies in subpopulations are being released and suggest an increased use of aromatase inhibitors when providers and patients are comfortable with the off-label use.

GnRH agonists

Leuprolide (Lupron—Abbott), a GnRH agonist, is most often used for infertility patients in conjunction with ovulation induction and COH. Leuprolide may be used in two ways.\textsuperscript{22} First, it may be used to suppress the body’s natural cycle, allowing for reproductive endocrinologists to control the cycle with exogenous hormones in COH. Unfortunately, among women who respond poorly to attempts at COH, this suppression may be too great and excessively high gonadotropin doses may be needed as a result. In these patients, micro-doses of leuprolide may be used. This second feature of leuprolide uses lower doses. Before leuprolide produces suppression, there is a surge of LH and FSH. If timing is correct, the presence of these hormones provides an additive effect to those provided by the reproductive endocrinologist. Therefore, dosing of leuprolide is quite variable when used with COH. Although studies suggest that the first option produces higher success rates,\textsuperscript{22} it is unclear whether this is a result of the regimen itself or the fact that the second protocol focuses on those who respond poorly to gonadotropins.

GnRH may be used alone in cases where overactive gonadotropins are contributing to endometriosis. In addition to leuprolide, goserelin (Zoladex—AstraZeneca) and nafarelin (Synarel—Pfizer) may be used for women with known endometriosis. Using GnRH agonists for 6 months or less to treat endometriosis is recommended. Because of the increased chance for cyst formation with the use of these agents, they should be started in the luteal phase if not being used with COH.\textsuperscript{28} Patients requiring long-term therapy are at risk for bone loss, but supplemental treatment with add-back estrogen and progesterone has limited this adverse effect.\textsuperscript{5} A detailed review of management of endometriosis is beyond the scope of the current work, but pharmacists interested in enhancing their knowledge of infertility should examine this topic further.

Gonadotropins

Exogenous gonadotropins are used to enhance ovarian function by providing additional FSH and/or LH activity. This enhanced function allows for the recruitment and development of multiple follicles. Several exogenous gonadotropins are available for use by injection: recombinant follitropin, including follitropin alfa (Gonal-f—EMD Serono) and follitropin beta (Follistim AQ—Organon);urofollitropin (Bravelle—Ferring); lutropin (Luvieren—EMD Serono); and menotropins (Menopur—Ferring and Reprofax—Ferring). IVF protocols using these treatments may start with low doses that step up. These protocols are likely more successful in limiting the occurrence of ovarian hyperstimulation syndrome (OHSS). These protocols typically start with doses of 50 to 75 International Units (IU) of FSH a day for 7 or more days, followed by regular dose increases. Alternatively, a step-down approach begins with 150 IU or more of FSH followed by regular dose decreases. The starting dose, frequency of dose change, and extent of dose change is specialized according to each provider/clinic. Vaginal ultrasounds and serum estradiol levels are used to monitor the progression of COH and may guide the reproductive endocrinologists on dosing decisions.\textsuperscript{22}

The most concerning adverse event related to the above medications used in ovulation induction/COH is OHSS.\textsuperscript{29} This adverse event is possible with any treatment used for the purpose of COH and may not be dose dependent. It is characterized by cystic enlargement of the ovaries and rapid fluid shifts from the intravascular compartment to the third space. Symptoms may be mild to severe and can include abdominal ascites, abdominal pain, sudden weight gain, pain or swelling in extremities, persistent nausea, and/or vomiting. Patients with PCOS are more likely to experience
OHSS. This condition is potentially life threatening, and women presenting to a pharmacy should be directed to contact their physician immediately or to visit the nearest emergency department. Maintenance of end-organ perfusion is critical and may require the use of anticoagulants in the most severe cases. Gonadotropins have similar adverse event profiles that may include headache, ovarian cysts, abdominal cramping, weight gain, nausea, vomiting, OHSS, and multiple gestations. Rare cases of thromboembolic and pulmonary conditions have been recorded in patients using gonadotropins. Injection site reactions are possible but are most common with urine-derived products.

**Recombinant follitropin**

Follitropin functions as FSH and is often referred to as recombinant FSH (rFSH). Both follitropin alfa (also alpha) and follitropin beta consist of two linked alpha and beta glycoprotein chains that are conjoined by electrostatic and hydrophobic forces and structurally identical to endogenous FSH. The nomenclature does not refer to the alpha and beta subunits but instead distinguishes one product from the other. Follitropin alfa was the first to market and, unlike follitropin beta, is purified by an immune-chromatographic technique. Follitropin alfa and beta are indicated for ovulation induction in patients with ovulation disorders or for use in IVF protocols. Both are recombinant FSH expressed from Chinese hamster ovary cells. Unlike urofollitropin, rFSH is free of urinary proteins, which could be allergenic.

**Urofollitropin**

Similar to recombinant FSH, urofollitropin (Bravelle—Ferring) also functions as FSH endogenously and is a highly purified form of urofollitropin. As with follitropin alfa and beta, when administered for 7 to 12 days, it stimulates the ovaries to produce multiple follicles. Urofollitropin is administered by either intramuscular or subcutaneous injection. It is purified from the urine of menopausal women. Allergic response is possible, though rare, because of the source of the proteins.

**Corifollitropin alfa**

Similar to recombinant FSH and urofollitropin, corifollitropin alfa functions as FSH in the body. It is not currently available in the United States but has received approval for use in European Union states. Corifollitropin alfa is a hybrid molecule with a prolonged half-life. It consists of the FSH alpha subunit and a hybrid of the FSH beta subunit and the C-terminal peptide of the HCG beta subunit. This agent should be more patient friendly as a result of the reduced number of injections required to sustain multifollicular growth. Two strengths of corifollitropin (100 and 150 mcg) are available outside of the United States based on patient weight above or below 60 kg, retrospectively.

Phase I trials reported no serious adverse events related to the drug and no changes in hematological or biological parameters. Injection site reactions were mild and infrequent. Phase II and III trials both reported similar adverse event profiles. The Phase III ENGAGE trial compared 150 mcg corifollitropin with 200 IU rFSH and demonstrated similar serious adverse events between the two agents. The occurrence of severe OHSS was 1.9% versus 1.2% for corifollitropin and rFSH, respectively. Headache, pelvic pain, and pregnancy-related complications were the most common adverse effects. Corifollitropin does not have proven efficacy over other forms of FSH. However, patients who are not at high risk of OHSS and would benefit considerably from a decreased number of injections (e.g., those who travel extensively for work) may prefer corifollitropin alfa.

**Lutropin**

Lutropin alfa (Luvieris—EMD Serano) is recombinant LH and is used only in patients with a rare condition of hypogonadotropic hypogonadism exhibiting profound LH deficiency. The mechanism of action is to stimulate the theca cells in the ovaries to stimulate androgen secretion, which is converted to estradiol by aromatase enzymes. This subsequently can trigger follicular development. It is approved for use with follitropin, and both medications are administered subcutaneously.

**Menotropins**

Menotropins (i.e., human menopausal gonadotropin [hMG]) were the first urine-derived preparation and were developed in the 1960s. Menotropins are a one-to-one ratio of FSH and LH. Highly purified menotropins (HP-hMG; Menopur—Ferring) and hMG (Repronex—Ferring) are indicated for ovarian development in women who have received GnRH agonist or antagonist pituitary suppression and who are enrolled in protocols for IVF or other assisted reproductive technology (ART). Menopur is extracted from the urine of postmenopausal women and purified. Each vial contains 75 IU FSH activity and 75 IU LH activity in a sterile, lyophilized form intended for reconstitution with 0.9% Sodium Chloride Injection. Repronex is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each vial contains 75 or 150 IU FSH and 75 or 150 IU LH in a sterile, lyophilized form. Repronex is administered by subcutaneous or intramuscular injection. Unlike follitropin, HCG, a naturally occurring hormone in postmenopausal urine, is detected in this product.

**Menotropins versus follitropin.** Several prospective and review studies have been conducted to evaluate whether recombinant menotropins or follitropin is preferred for COH. Studies have evaluated which therapy produces higher numbers and quality of follicles and higher number of live births, as well as cost considerations. In 2008, Coomarasamy et al. selected seven studies and found a significant increase in favor of menotropins for number of live births. In 2009, Al-Inany et al. reviewed six studies of 2,371 patients to assess whether either treatment produced better pregnancy rates. The authors concluded that menotropins produced a better pregnancy rate in standard IVF cycles and borderline improvement in patients not undergoing IVF. However, the menotropins did not produce an improved pregnancy rate in patients having IVF with ICSI. The reason for this difference was unclear.

In 2010, Lehert et al. published a meta-analysis of 16 studies and 4,040 patients to evaluate which therapy produces more oocytes with a lower total dose per cycle. This primary endpoint directly relates to the role of the product. The investigators believed that making comparisons regarding pregnancy was too difficult for primary consideration because of multiple factors that varied among trials. Prospective randomized or quasirandomized
controlled trials were included, irrespective of concomitant use of GnRH agonists or antagonists. Dosing and duration of treatment was not consistent among the included trials. Studies that included patients with PCOS were excluded from the main analysis. Secondary endpoints included the total dose of gonadotropins, clinical pregnancy rate, OHSS, and live birth rate, if available. Significantly fewer oocytes were retrieved in the menotropins treatment arm and the total dose of menotropins was higher. The difference in pregnant rates and OHSS cases were not significant between treatments.31

Because of lack of control of baseline characteristics, variability among treatment dose and duration, and postrandomization management, determining which treatment is more effective and cost effective in COH is difficult. Additional prospective trials and subsequent analysis are needed to better evaluate which treatment will produce the best results for specific populations.

**HCG**

HCG (u-HCG; Novarel—Ferring and Pregnyl—Organon) and HCG alfa (r-HCG; Ovidrel—EMD Serano) are approved by FDA for ovulation induction. Administration of HCG follows the use of gonadotropins, aromatase inhibitors, or clomiphene citrate. It mirrors the normal menstrual cycle and the normal LH surge occurring before ovulation. This completes the final steps of follicular development and triggers ovulation.23 It also promotes the development of the corpus luteum and the production of testosterone.35 A single HCG is usually timed 36 hours before scheduled oocyte retrieval when used with IVF. One or more additional doses may also be ordered for administration at specific times. Patients should be advised that this timing is very important and should notify their physician if they must deviate from the schedule. Urine-derived products (Novarel and Pregnyl) are supplied as 10,000 units and given intramuscularly. Recombinant HCG is supplied as 250 mcg and is administered subcutaneously.32 The formulations have comparable efficacy.23 Recombinant HCG is preferred by patients because of the ability for subcutaneous administration.

**GnRH antagonists**

GnRH antagonists such as cetrorelix (Cetrotide—EMD Serano) and ganirelix (brand name off market) are used to suppress LH production at the pituitary level. This allows the LH surge to be managed by the fertility specialist. Cetrorelix or ganirelix 0.25 mg per day starting on day 7 until HCG administration may be administered during early to late follicular phase until HCG administration. In addition, a single dose of cetrorelix 3 mg on during days 5 through 9 can also be used.23,41,44 These protocols are primarily used in patients who respond poorly to other treatment protocols involving GnRH agonists and gonadotropins alone. Studies have demonstrated that antagonist trials may be especially useful in patients with OHSS risk because significantly fewer cases of OHSS have been reported in patients receiving GnRH antagonists than in those receiving GnRH agonists.30

**Medications for purposes other than direct ovulation induction and COH**

**Metformin.** Metformin (Glucophage—Bristol-Myers Squibb) can be used as an adjunctive treatment in women with infertility caused by PCOS secondary to hyperinsulinemia. Although this is a commonly used therapy, it does not have FDA approval for this indication. Studies suggest that use of metformin in addition to clomiphene citrate in women with PCOS increases the frequency of spontaneous ovulation, menstrual cyclicality, and ovulatory response to clomiphene citrate.7 Metformin improves insulin sensitivity by reducing absorption of glucose and reducing hepatic glucose production. This leads to a reduction in hyperinsulinemia, which in turn reduces excess androgen production by the ovaries and reduces production of LH in the pituitary.45,46

**Dopamine agonists.** Bromocriptine (Parlodel—Novartis) is approved by FDA to treat hyperprolactinemia associated with amenorrhea with or without galactorrhea, infertility, or hypogonadism. This medication should only be used in patients with elevated prolactin levels. Bromocriptine is used to reduce plasma levels of prolactin, increase GnRH secretion, and induce ovulation, thereby restoring fertility.47-49 Cabergoline (brand name no longer available), is a selective dopamine receptor type 2 agonist also approved for treating hyperprolactinemia. This treatment has fewer adverse effects and greater potency than bromocriptine, suggesting that cabergoline is a better treatment choice. However, longer term use may increase the risk of hypertrophic valvular heart disease; therefore, bromocriptine may be considered the safer choice.3

**Progesterone.** Progesterone is commonly used to provide luteal (postovulation) phase support. Progesterone provides many functions related to fertility, including preparing and maintaining the uterine lining, and may prevent early miscarriage. This may be especially important following other fertility agents, which may affect the body’s ability to produce progesterone. It may also be used in patients whose ovaries do not produce enough progesterone or produce follicles that do not secrete enough progesterone. Patients with recurrent early pregnancy loss may especially benefit from the addition of progesterone. Progesterone is available in multiple dosage forms, including a vaginal gel (Crinone—Watson), vaginal suppository (compounding kit—CurtisPharma), vaginal inserts (Endometrin—Ferring), oral capsules inserted in the vagina (Prometrium—Curtis Abbott), and an oil-based solution injection. Studies have examined the use of injectable formulations versus vaginal/oral formulations, as well as comparison of different vaginal dosage forms. Most studies have not shown a conclusive best choice; however, vaginal treatments are preferred because of injection site reactions and patient adherence/tolerance.41,49 Oral administration of progesterone (Prometrium) is classified in Pregnancy Category B and is contraindicated in pregnancy because of the possibility of hypospadias and other possible congenital anomalies during pregnancy.30 Other forms of progesterone do not have this warning. Pharmacy computer systems may alert the pharmacist to this contraindication. Pharmacists must ensure that patients understand these risks and benefits.

**Aspirin.** Some physicians may start patients on aspirin (81-325 mg) before treatment procedures. Published studies show limited usefulness but have investigated a possible effect on uterine blood flow and uterine clotting and in reducing OHSS. Safety data also indicate that using aspirin during conception is
not a pregnancy or fetus risk and that patients may need counseling to clarify the pregnancy warning with this medication.51

Nonpharmacologic treatment methods

Ovulation induction/COH

Ovulation induction includes the use of FSH, LH, or combination treatment to induce maturation and release of follicles. Ovulation induction may be used with normal intercourse or with ART. COH involves ovulation induction to produce multiple follicles and increase the likelihood of success or allow cryopreservation of embryos. No specific algorithm, standard, best practice, or published guideline has been established. Before ovulation induction, the normal reproductive system is often down regulated by the use of oral contraceptives or GnRH agonists. This allows the reproductive endocrinologist greater hormonal regulation and control.

ARTs

IUI. IUI requires the insertion of sperm with a pipette into the uterus to improve fertilization. The procedure is performed in a regular exam room following ovulation induction. Before insemination, the sperm sample is cleaned and concentrated to improve fertilization. Controversy exists regarding whether clomiphene citrate, aromatase inhibitors, or gonadotropins are the best pharmacologic treatment with IUI.

IVF. IVF requires the surgical retrieval of mature eggs from a woman’s ovaries. Then, in the laboratory, the eggs are fertilized with a man’s sperm. Typically, 3 to 5 days after fertilization, the embryos are implanted into the uterus. IVF is usually recommended in women with bilateral fallopian tube blockage. It is also used for other conditions causing infertility, including endometriosis, unexplained infertility, cervical factor infertility, male factor infertility, and ovulation disorders. Women undergoing IVF have an increased likelihood of having multiple births. This is a risk because multiple fertilized embryos are often implanted into the uterus to increase the chance of conception. A variety of different treatment protocols are used by different clinics around the country. Patients are carefully monitored for an appropriate number of mature oocytes and OHSS. Patients receiving treatments may have daily office visits as they approach retrieval, which may require regular dose adjustment by a reproductive endocrinologist.

ICSI. ICSI is a procedure in which a single sperm is injected directly into an egg to achieve fertilization. Although this relates more to male factor infertility, this technique is done in conjunction with the standard IVF procedures. It is especially useful in patients who have previously failed conception with standard techniques.

Donor eggs and sperm. The use of egg donation is commonly used for women who are unable to conceive because of a decline in ovarian function. This usually occurs as a result of advancing age but may be independent of age. The woman donating the eggs undergoes ovarian stimulation, allowing her to produce multiple eggs. A transvaginal ultrasound is used to monitor follicle growth. The eggs are removed through a small needle passing through the vaginal wall. The woman receiving the donation has her cycle controlled using hormones, ensuring that her uterus is ready for implantation at the proper time.52

Emotional component of infertility and additional resources

Infertility affects a patient’s health and her emotional well-being. Infertility can greatly affect the relationship of the couple and relationships with friends and family. It can also cause a variety of emotions, such as feeling inadequate, embarrassed, or disengaged. In a study conducted by GfK Roper on behalf of Schering-Plough and Merck, 80% or more men and women said they would have sought treatment sooner if they could do it over again.53 Although the majority of couples felt that the struggle to conceive had brought them closer together (58%) and more than 80% of women praised their partner for being supportive throughout the process, 55% of couples reported that intimacy became physically and emotionally anxious. Patients reported feeling “despair and loss that can’t be quantified,” “fear that life will be eternally empty,” and not being able to “handle other people being emotionally invested.”54 Members of RESOLVE, a U.S. infertility association for patients, professionals, and media, have criticized that attention to infertility often focuses on success stories despite the fact that infertility treatment is not always a success. Although some patients will never be cured of infertility, discussing treatment failure is uncommon. Many patients have called for more recognition, funding, and support so that more couples experiencing infertility can get help.

Fully understanding what individual patients are experiencing when dealing with infertility and its treatments is difficult and challenging. It is extremely important for pharmacists to provide appropriate medication counseling. Also, if patients are willing to discuss the situation, listening and being empathic is critically important.

A variety of books, websites, and online communities are available for information on infertility. In addition to its online tools, the resolve network also has local meeting groups. Pharmacists are encouraged to consult www.resolve.org to see whether infertility support groups are available in the community and, if so, to make this information available to patients.

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TREATING INFERTILITY REVIEWS

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1. Which of the following is the least common diagnosis in female infertility?
   a. Ovulatory disorders
   b. Tubal and pelvic disorders
   c. Unexplained infertility
   d. Chromosomal abnormalities

2. Which of the following risk factors is related to the determination that a patient should seek treatment for infertility?
   a. Increased age
   b. Tobacco or alcohol use
   c. Increase caffeine intake
   d. Increased or decreased body weight

3. All of the following would be possible treatments for a patient experiencing WHO (World Health Organization) group I anovulation except:
   a. Clomiphene citrate.
   b. Gonadotropin-releasing hormone (GnRH) agonist.
   c. Gonadotropins.
   d. In vitro fertilization (IVF).

4. Which of the following is a common adverse effect of clomiphene citrate?
   a. Headache
   b. Tachycardia
   c. Hyperglycemia
   d. Bone pain

5. Which of the following medications is used to trigger ovulation?
   a. Clomiphene citrate
   b. Bromocriptine
   c. Human chorionic gonadotropin
   d. Gonadotropins

6. When counseling patients on infertility treatments, it is important to:
   a. Consider that the medication may be used outside its usual indication.
   b. Assure them that the medication will lead to success in conceiving.
   c. Require them to discuss the details of their infertility issues.
   d. Suggest that they consider adoption.

7. Progesterone is primarily used for which of the following?
   a. Inducing ovulation
   b. Luteal phase support
   c. Treatment of endometriosis
   d. Treatment of hyperprolactinemia

8. Which of the following is a characteristic of ovarian hyperstimulation syndrome (OHSS)?
   a. Its most common initial symptom is dizziness.
   b. It is less likely to occur in patients with polycystic ovary syndrome (PCOS).
   c. It is always dose dependent.
   d. It can be life threatening.

9. Which of the following is a symptom of OHSS?
   a. Hot flashes
   b. Swelling of extremities
   c. Mood swings
   d. Itching

10. A patient who visits your pharmacy regularly confides that she has been trying to conceive for 2 years. Which of the following actions would be appropriate for you to take?
    a. Discuss available diagnostic testing and determine what tests have been completed.
    b. Inform the patient that she is likely facing treatment with IVF and you can assist with selecting the best treatment.
    c. Inform the patient that she is unlikely to become pregnant because of a specific risk factor.
    d. Describe the adverse effects associated with fertility medications so the patient is prepared.

11. Which of the following is true regarding the use of follitropin in female infertility?
    a. Follitropin alfa is structurally different than follitropin beta.
    b. Follitropin contains follicle-stimulating hormone (FSH) and luteinizing hormone (LH).
    c. Follitropin is a GnRH antagonist.
    d. Follitropin is often referred to as recombinant FSH.
12. GnRH antagonists are used to:
   a. Suppress production of LH in the pituitary.
   b. Shrink endometrial lesions.
   c. Support patients with PCOS.
   d. Treat hyperprolactinemia.

13. Which of the following is a characteristic of menotropins?
   a. They consist of a combination of LH and FSH.
   b. They are clearly more efficacious than follitropin in controlled ovarian hyperstimulation.
   c. After reconstituting, they can be refrigerated and used for multiple doses.
   d. They have a high rate of drug interactions when used with other fertility drugs.

14. Which of the following is a correct statement about fertility medications?
   a. Most fertility medications can be given safely during pregnancy because they are derived from naturally occurring hormones.
   b. HCG can be used to treat endometriosis, but this is considered an off-label use.
   c. Patients should have a complete fertility evaluation before initiating any medications.
   d. Patients receiving fertility treatment have a high frequency of adverse effects.

15. Which of the following statements is correct regarding the use of GnRH agonists?
   a. Depot forms are used for treating endometriosis.
   b. GnRH agonists produce a protective effect on bone density.
   c. Hot flashes are not commonly seen with GnRH agonists.
   d. Clomiphene citrate belongs to this medication class.

16. Which of the following is used to assess ovarian reserves?
   a. Anti-Müllerian hormone
   b. TSH
   c. Basal body temperature
   d. Prolactin level

17. Which of the following is true regarding preparation of gonadotropins for injection?
   a. Reconstituted medications will still be cloudy after reconstitution.
   b. Patients should prime prefilled pens before the first use.
   c. Powder should be shaken while reconstituting.
   d. Patients do not need to rotate the site of injection.

18. Which of the following statements is correct regarding the use of progesterone in infertility treatment?
   a. If the fertility treatment is successful, progesterone treatment will usually continue into the first trimester of pregnancy.
   b. Oral administration of progesterone is the preferred route for infertility treatment.
   c. Progesterone should not be given to patients with an allergy to eggs.
   d. Progesterone may diminish the effects of antidiabetics agents.

19. Which of the following statements is correct regarding clomiphene citrate?
   a. It is recommended for an indefinite number of cycles.
   b. Concurrent use of St. John’s wort may decrease efficacy.
   c. It results in increased levels of FSH and LH.
   d. Doses are typically 5–10 mg daily.

20. Which of the following is true of infertility?
   a. All patients follow a very similar course of pharmacotherapy and procedures.
   b. Efficacy of a given pharmacologic agent is similar in all patients.
   c. Efficacy of a given pharmacologic agent is similar among all patients with the specific diagnosis such as tubal factor.
   d. All patients can benefit from having a pharmacist available who is willing to discuss treatment without passing judgment.