FERTILITY

Three recent recommendations, on clomiphene, immunization, and postsurgical adhesions, may affect how you practice. These experts get to the heart of the guidelines.

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Dr. Adamson reports that he receives grant or research support from Auxogyn and LabCorp, is a consultant to Palo Alto Medical Foundation, and has other financial relationships with Advanced Reproductive Care, Auxogen, and LabCorp.

Dr. Abusief reports no financial relationships relevant to this article.

These experts discuss three recent American Society for Reproductive Medicine Committee Opinions. The first is on the optimal use of the most widely prescribed medication for fertility, clomiphene citrate. The second highlights the currently recommended vaccinations for women who are of reproductive age. And the third is on the current evidence for prevention of postsurgical adhesions, which have the potential to cause infertility. Their discussions could affect how you approach your infertile patients.

Safe, effective use of clomiphene

Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in infertile women: A committee opinion. Fertil Steril. 2013;100(2):341–348.

Clomiphene citrate (CC) is the fertility medication most commonly used by gynecologists. However, important principles in its use often are not followed, resulting in suboptimal patient care. The American Society for Reproductive Medicine published a recent Committee Opinion on CC's indications, use, and alternative treatments. We summarize the essential aspects of CC use.

Who should be treated?

CC can be used to treat both anovulation/oligo-ovulation and unexplained infertility, but it is not effective in hypothalamic amenorrhea or hypergonadotropic hypogonadism (usually premature ovarian insufficiency). Anovulation/oligo-ovulation may be due to polycystic ovary syndrome (PCOS), obesity,

hypothalamic dysfunction related to eating disorders, weight, exercise, stress, hyperprolactinemia, pituitary tumors, or thyroid disease. The exact cause is often indeterminable, however.

There is no evidence CC is effective treatment for "luteal phase defect." Unexplained infertility also can be treated with CC with intrauterine insemination (IUI).[1]

Pretreatment evaluation

Diagnosis of ovulatory dysfunction is usually made by menstrual history alone (normal menses, ≥24 and ≤35 days). Testing with luteal phase serum progesterone or serial transvaginal ultrasound generally is unnecessary.

Use the history, physical examination, and other testing, as necessary, to rule out other endocrinopathies, including diabetes mellitus (screening for impaired glucose tolerance), thyroid disorders (measurement of thyroid-stimulating hormone, or TSH), hyperprolactinemia (prolactin assessment), congenital adrenal hyperplasia (measurement of 17-alpha hydroxyprogesterone acetate), and virilization (assessment of testosterone and dehydroepiandrosterone sulfate, or DHEA-S).

If disease-specific treatment does not result in normal ovulation, then CC can be used. Although it may be difficult for them, obese women should be encouraged to lose weight. In infertile couples with a normal menstrual cycle and no other identifiable infertility factors, if hysterosalpingogram and semen analysis are normal, treatment of their unexplained infertility with CC and IUI may be effective. Ovulation induction or ovarian stimulation has little benefit when severe male, uterine, or tubal factors are present.

Treatment regimens

CC is usually given 50 mg/day orally for 5 days starting on the second to fifth spontaneous or progestin-induced menstrual cycle day, with equivalent treatment outcomes regardless of start day 2, 3, 4, or 5. If the patient's response to this dose is inadequate, treatment can be increased 50 mg/day in each subsequent cycle, to a maximum of 250 mg/day. However, the maximum FDA-approved dose is 100 mg/day, and only 20% of patients respond when given doses higher than this. Obese patients may respond at the higher doses.

The luteinizing hormone (LH) surge occurs 5 to 12 days after the last CC dose is taken. There is no benefit to giving human chorionic gonadotropin (hCG) if the patient has a spontaneous LH surge. The pregnancy rate might actually be reduced by 25% when hCG is given unnecessarily.[2]

In anovulatory/oligo-ovulatory women, there is no benefit of IUI over timed intercourse for achieving pregnancy. For unexplained infertility, however, CC with timed intercourse does *not* appear effective, but CC combined with IUI *is* effective.[3] Timed intercourse should occur approximately every 2 days (1–3 days) starting about 3 to 4 days before expected ovulation.

Treatment should continue 3 to 4 months. Younger patients (<35 years) with a short duration of infertility (<2 years) who respond to CC can receive up to 6 months of treatment. Treatment beyond 6 months is not recommended.

Ovulation and pregnancy rates

Half of anovulatory/oligo-ovulatory women will ovulate with a 50-mg dose of CC and half of the remaining will ovulate with a 100-mg dose. Among women who ovulate with CC, cumulative pregnancy rates for 50 mg/day, 100 mg/day, or 150 mg/day at 3 months are 50%, 45%, and 33%, respectively, and at 6 months are 62%, 66%, and 38%, respectively. In general, a 55% to 73% pregnancy rate can be expected.[4] Increasing age, duration of infertility, and obesity are associated with lower pregnancy rates and treatment failure.

Alternative and adjunctive regimens

For patients who are not using progestin to induce menses and who have not responded with ovulation by day 14 to 21, longer courses of CC treatment (7 to 8 days) and a step-up protocol to the next highest CC dose are alternative regimens that may work in some cases.

Some anovulatory or oligo-ovulatory women with PCOS who do not respond to CC

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Among anovulatory women who ovulate with clomiphene treatment, 50% will be pregnant at 3 months and 62% at 6 months

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alone may respond to CC combined with metformin at 1,500 to 1,700 mg/day. Metformin combined with diet and exercise for weight loss is recommended. Metformin is associated with gastrointestinal side effects and rare hepatic toxicity or lactic acidosis; therefore, liver and renal functions should be assessed prior to treatment and monitored afterward.

Women with DHEA-S serum concentrations of 200 µg/dL or greater, and even some women with normal DHEA-S levels, may be more responsive to CC and achieve higher pregnancy rates when given dexamethasone 0.5 mg/daily on cycle days 3 to 12. Glucocorticoids have significant side effects and should be discontinued if treatment is unsuccessful or when pregnancy occurs.

Some CC-resistant anovulatory women and women with unexplained infertility may benefit from a trial of sequential CC/gonadotropin treatment consisting of standard CC treatment followed by human menopausal gonadotropins (hMG) or follicle-stimulating hormone (FSH) 75 to 150 IU/day for 3 days. Some, but not all, studies show pregnancy rates in these patients equivalent to those undergoing gonadotropin treatment alone (at a reduced cost). There are no studies directly comparing the treatment regimens, however, and risks of multiple pregnancy might be increased for patients taking both CC and gonadotropin, so this treatment should only be provided by clinicians with requisite training and experience.

Other alternatives to CC therapy in CC-resistant patients include aromatase inhibitors, tamoxifen, insulin-sensitizing agents, ovarian drilling, gonadotropins, and in vitro fertilization.

Monitoring of CC cycles

Objective evidence of ovulation is key to successful treatment. Ovulation predictor kits are more than 90% successful, if used properly, in identifying the LH surge 5 to 12 days after CC is finished (usually around cycle day 16 or 17). Ovulation occurs about one-half day to 2 days after the LH surge. Serum progesterone is the most certain test of prior ovulation (other than pregnancy) but cannot predict time of ovulation. Serial ultrasound shows the size and number of follicles and presumptive ovulation with follicle collapse, as well as echogenic corpus luteum and cul de sac fluid, but it is expensive and often not cost-effective.

It is prudent to postpone further treatment if the patient has large ovaries or a cyst, but routine baseline ultrasound monitoring is no longer considered necessary. However, regular contact with the patient should be maintained to review response to treatment and to ensure that any additional or alternative treatments are not delayed.

Side effects of CC treatment

Mood swings, visual disturbances, breast tenderness, pelvic discomfort, and nausea are reported in less than 10% of patients. Mild ovarian hyperstimulation syndrome (OHSS) is not uncommon, but severe OHSS is rare.

The major risk to CC treatment is twin (8% risk) and triplet (0.5% risk) pregnancies. There is no evidence of increased risk of congenital anomalies, miscarriage, or ovarian cancer.[1,5,6]

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Clomiphene treatment, whose greatest risk is twin and triplet pregnancies, should not be continued for more than 3 to 6 months

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1. Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in infertile women: A committee opinion. Fertil Steril. 2013;100(2):341–348.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

All gynecologists should be able to diagnose and treat infertility with clomiphene. It is effective for many patients with anovulatory/oligo-ovulatory infertility, and also for unexplained infertility when combined with IUI. Careful evaluation of fertility and endocrinologic status is necessary before treatment, as is monitoring during treatment. Although this treatment may appear to be simple, there are many important principles that need to be followed if treatment is to be effective and safe, and if the patient is to receive quality infertility care. Treatment is safe, (the major risk is multiple pregnancy) but should not be continued for more than 3 to 6 months.

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Strive for prepregnancy vaccination

Practice Committee of American Society for Reproductive Medicine. Vaccination guidelines for female infertility patients: A committee opinion. Fertil Steril. 2013;99(2):337–339.

Patients presenting for fertility treatment may have incomplete or unknown immunization status. Encounters with women who desire conception offer an opportunity for providers to optimize their patients' health prior to pregnancy. Vaccination before or, when appropriate, during pregnancy protects women from preventable disease, decreases the risk for vertical fetal transmission, and enables the passage of maternal immunoglobulins to the fetus, conferring passive immunity to the newborn.

National standards for vaccination have been established by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC). This yearly updated vaccination schedule is available at the CDC's Web site (http://www.cdc.gov/vaccines/schedules/hcp/adult.html).[1] Ideally, a woman's immunization status should be evaluated and made complete prior to pregnancy. Some vaccines are safe and appropriate for administration during pregnancy, provided the benefits clearly outweigh the risks. The recommended vaccines during pregnancy include inactivated influenza (seasonal and H1N1) and the combined tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap).

Many physicians avoid giving vaccinations during pregnancy because of the concern that a spontaneous abortion or congenital anomaly might be incorrectly attributed to vaccine administration, but few vaccines are contradicted during pregnancy. Those that are contraindicated are those containing live virus, including measles, mumps, and rubella (MMR); varicella; and herpes zoster. Concerns also have been raised regarding the safety of administering influenza vaccines containing the mercury-based preservative thimerosol. However, no scientific evidence has conclusively linked adverse effects on offspring with thimerosol-containing vaccines administered during pregnancy.

Immunizations recommended for women of reproductive age

Measles, mumps, rubella (MMR). This vaccine is recommended for all women lacking confirmed immunity to rubella. The vaccine contains live, attenuated virus and is given as a single dose. Women should avoid pregnancy for 1 month after vaccination.

Varicella. This vaccine is for all women lacking confirmed immunity to varicella. It also contains a live, attenuated virus. It is administered in two doses, 1 month apart, and women should avoid pregnancy for 1 month after vaccination.

Influenza. The flu vaccine is recommended annually for individuals 6 months of age and older. The injectable vaccine contains inactivated virus and may be administered during pregnancy—at any time but optimally in October or November because the flu season occurs January through March. (The intranasal influenza vaccine contains live, attenuated virus and should be avoided in pregnancy.) Either method is administered as a single dose.

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Few vaccines are contraindicated in pregnancy, but many physicians avoid vaccination during pregnancy to avoid potential complications being attributed to vaccination

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Non-routine vaccines indicated prior to or during pregnancy in high-risk patients

Vaccine	Description	Indications
Pneumococcus	Contains surface capsular polysaccharides from pneumonia serotypes most likely to cause active disease	Indicated prior to pregnancy for patients with asplenia, diabetes, sickle cell anemia, chronic cardiovascular/pulmonary disease, or immunocompromise (HIV, malignancy)
Hepatitis A	Contains inactivated virus	Indicated during pregnancy for patients who have chronic liver disease, are planning travel to areas with a high prevalence of hepatitis A infection, are receiving clotting factor concentrates, are intravenous (IV) drug users, or who work with hepatitis A virus in a laboratory setting
Hepatitis B		Can be administered during pregnancy to high-risk individuals, including women living in the same household as someone who has a known hepatitis B infection (including a sexual partner), health-care workers exposed to blood or blood products, women planning travel to areas with a high prevalence of hepatitis B infection, patients receiving hemodialysis or clotting factors, IV drug users, and women with sexually transmitted infections or multiple sexual partners
Meningococcus		Indicated prior to pregnancy for high-risk patients, including those living in areas with a high prevalence of meningococcus (sub-Saharan Africa, parts of the Middle East, college dormitories)

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Ensuring adequate vaccination prior to pregnancy is an essential step of infertility treatment

Thimerosal is a mercury-based preservative used in vaccines, including the influenza vaccine, and is appropriate for use in pregnant women; studies have not shown an association between vaccines containing thimerosal and adverse effects in pregnant women or their offspring.

Tetanus-diptheria-pertussis (Tdap) and tetanus-diphtheria (Td). Tdap or Td is recommended for adults aged 19 to 64 years who have or anticipate having close contact with an infant less than 12 months of age. Due to the recent increase in pertussis infection, Tdap should be given to all women who have not previously received the vaccine and who are pregnant or might become pregnant. It can be given anytime during pregnancy, but optimal administration is during the third trimester or late second trimester (after 20 weeks' gestation) to confer the greatest amount of fetal protection.

If the vaccine is not being administered during pregnancy, it should be given in the immediate postpartum period to ensure pertussis immunity and to reduce transmission to the newborn. Tdap is administered as a single dose of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Vaccination is a very important aspect of pre-pregnancy care but is especially important for infertile women who desire pregnancy. Planning of infertility treatment should include assessment of the patient's vaccination status and completion of appropriate vaccinations before infertility treatment is initiated.

Non-routine vaccines include pneumococcus, hepatitis A, hepatitis B, and meningococcus (**TABLE**). These vaccines should be administered as indicated in high-risk patients.

Health-care providers caring for women with infertility are urged to assess patients' immunization status prior to attempting pregnancy, to counsel patients about the importance of protecting them and their potential offspring from preventable disease, and to facilitate vaccination prior to conception attempts.

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1. Adult immunization schedules. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/vaccines/schedules/hcp/adult.html. Updated October 19, 2013. Accessed January 16, 2014.

Do current options effectively prevent postsurgical adhesions?

Practice Committee of American Society for Reproductive Medicine in collaboration with Society of Reproductive Surgeons. Pathogenesis, consequences, and control of peritoneal adhesions in gynecologic surgery: A committee opinion. Fertil Steril. 2013;99(6):1550–1555.

Postoperative adhesions are a natural consequence of surgery and a major problem in gynecology. They may cause postsurgical infertility, abdominal/pelvic pain, or bowel obstruction as well as complicate subsequent surgeries by increasing operative times and the risk of bowel injury. The American Society for Reproductive Medicine (ASRM) and the Society of Reproductive Surgeons (SRS) recently evaluated the epidemiology, pathogenesis, and clinical consequences of adhesion formation and the evidence behind strategies for reducing adhesion formation.

In their joint Committee Opinion, they noted that open and laparoscopic approaches to surgery carry comparable levels of risk for adhesion-related hospital readmission. Ovarian surgery has the highest risk for adhesion-related readmission, at 7.5 per 100 initial operations, and the incidence of small bowel obstruction after hysterectomy was found to be 1.6 per 100 procedures. Adhesion-related US health-care costs are estimated at approximately $1 billion annually.

The Societies noted that more severe adnexal adhesions are associated with lower pregnancy rates, and treatment of adnexal adhesions appears to improve pregnancy rates. Investigators found adhesions to cause about three-quarters of postoperative small bowel obstructions; however, the relationship between adhesions and pelvic pain remains unclear. It is thought that adhesions may cause visceral pain by impairing organ mobility, but there is no relationship between the extent of adhesions and the severity of pain. It appears that only dense adhesions involving the bowel are associated with chronic pelvic pain. Predicting the outcome of lysis of adnexal or bowel adhesions is difficult.

Reduction of adhesion formation

Theoretically, adhesions may be reduced by minimizing peritoneal injury during surgery, avoiding intraoperative reactive foreign bodies, reducing local inflammatory response, inhibiting the coagulation cascade and promoting fibrinolysis, or by placing barriers between damaged tissues.

Careful surgical technique includes gentle tissue handling, meticulous hemostasis, excision of necrotic tissue, minimizing ischemia and desiccation, using fine and nonreactive suture, and preventing foreign-body reaction and infection, all "microsurgical principles."

ASRM and SRS reported that the surgical approach (laparoscopy vs laparotomy) is much less important than the extent of tissue injury. However, laparoscopy may result in less tissue and organ handling and trauma, avoid contamination with foreign bodies, enable more precise tissue handling, and result in less postoperative infection. The pneumoperitoneum has a tamponade effect that facilitates hemostasis during laparoscopy, but the process also can be associated with peritoneal desiccation and reduced temperatures that can increase injury.

Laparoscopic myomectomy was found to have a 70% risk of postoperative adhesions, compared with a 90% risk after laparotomy. It is unclear whether peritoneal closure at laparotomy reduces or increases adhesions, but parietal peritoneal closure at primary cesarean delivery results in fewer dense and filmy adhesions.

Adjuncts to surgical technique

ASRM and SRS reported on three adjuncts to surgical technique that have been proposed

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The extent of tissue injury is more important than the surgical approach when considering postoperative adhesions

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FDA-approved surgical adhesion barriers may help decrease adhesions postoperatively, but microsurgical principles also should be utilized to reduce adhesions

to reduce the risk of postoperative adhesions: anti-inflammatory agents, peritoneal instillates, and adhesion barriers.

Dexamethasone, promethazine, and other local and systemic anti-inflammatory drugs and adhesion-reducing substances have not been found effective for reducing postoperative adhesions.

Peritoneal instillates—which create "hydroflotation" and include antibiotic solutions, 32% dextran 70, and crystalloid solutions such as normal saline and Ringer's lactate with or without heparin or corticosteroids—have not been found effective.[1] Icodextrin 4% (Adept Adhesion Reduction Solution, Baxter Healthcare) is FDA approved as an adjunct to good surgical technique for the reduction of postoperative adhesions in patients undergoing gynecologic laparoscopic adhesiolysis. However, a systematic review concluded that there is insufficient evidence for its use as an adhesion-preventing agent.[1]

Adhesion barriers may help reduce postoperative adhesions but cannot compensate for poor surgical technique. Although the bioresorbable membrane sodium hyaluronic acid and carboxymethyl cellulose (Seprafilm, Genzyme Corp) is FDA-approved, there is limited evidence that it prevents adhesions after myomectomy.[2] Because it fragments easily, it is mostly used at laparotomy.

Oxidized regenerated cellulose (Interceed, Ethicon Women's Health and Urology) is an FDA-approved absorbable adhesion barrier for use at laparotomy that requires no suturing and has been shown to reduce the incidence and extent of new and recurrent adhesions at both laparoscopy and laparotomy by 40% to 50%, although there is little evidence that this improves fertility.[2] Complete hemostasis must be achieved to use Interceed, and the addition of heparin confers no benefit.

Another product is expanded polytetrafluoroethylene (ePTFE, Gore-Tex Surgical Membrane, WL Gore and Associates), a nonabsorbable adhesion barrier produced in thin sheets and approved by the FDA for peritoneal repair. ePTFE must be sutured to tissue and helps prevent adhesion formation and reformation regardless of the type of injury or whether complete hemostasis has been achieved. In a small trial, it decreased postmyomectomy adhesions.[3] ePTFE also was more effective than oxidized regenerated cellulose in preventing adhesions after adnexal surgery.[4] Its use has been limited by the need for suturing and later reoperation for removal, although it probably does not have to be removed if it will not interfere with normal organ function since it has been used as a pericardial graft for many years.[5]

Hyaluronic acid (HA) solution (Sepracoat, Genzyme) is a natural bioabsorbable component of the extracellular matrix. Women undergoing laparotomy have fewer new adhesions with HA solution, but it is not approved for use in the United States.[6] Polyethylene glycol (PEG; SprayGel, Confluent Surgical) was effective in early clinical trials but is not FDA-approved.[5] Fibrin sealant (Tisseel VH, Baxter Healthcare) has been reported to decrease the formation of adhesions after salpingostomy, salpingolysis, and ovariolysis. Because it is a biologic product derived from human blood donors, it poses a risk for transmission of infectious agents. It is FDA-approved for use in cardiothoracic

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WHAT THIS EVIDENCE MEANS FOR PRACTICE

Adhesions are the most common complication following gynecologic surgery, and they pose potential longstanding consequences to patients. There is no evidence that anti-inflammatory agents reduce postoperative adhesions and insufficient evidence to recommend peritoneal instillates. FDA-approved surgical barriers reduce postoperative adhesions but there is not substantial evidence that their use improves fertility, decreases pain, or reduces the incidence of postoperative bowel obstruction. All gynecologists need to understand the importance of using microsurgical principles rather than relying on adhesion barriers to reduce postoperative adhesions.

surgery, splenic injuries, and colostomy closure for hemostasis.

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