FERTILITY

The state of the art in 5 key areas, with recommendations from ASRM and other experts

G. David Adamson, MD
Director, Fertility Physicians of Northern California, Palo Alto and San Jose, Calif, Adjunct Clinical Professor, Stanford University, and Associate Clinical Professor, University of California San Francisco

Dr. Adamson is a past president of the Society for Assisted Reproductive Technology, the Society of Reproductive Surgeons, the Pacific Coast Reproductive Society, and the American Association of Gynecologic Laparoscopists (AAGL), and is President-elect of the American Society for Reproductive Medicine

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The treatment of infertility has advanced rapidly over the past 25 years, thanks to technological developments and improved application of evidence-based clinical algorithms. Many tests and treatments that once were common no longer are, while rising in vitro fertilization (IVF) success rates and other laboratory procedures have transformed many aspects of management.

Changes are occurring so quickly it is often difficult for the general ObGyn to know the most advanced and appropriate treatment for a given patient. The American Society for Reproductive Medicine (ASRM) Practice Committee establishes guidelines based upon well-designed studies to help physicians keep abreast of the best clinical practices. In this article, I focus on recent ASRM guidelines in 5 topical areas associated with substantial misinformation in both the professional and public sectors:

- when and how gynecologists should initiate infertility testing and treatment
- how to evaluate and manage recurrent pregnancy loss
- the need to reduce the rate of multiple gestation from IVF and ART
- the expanded applications for preimplantation genetic diagnosis
- the truth about fertility-sparing efforts in young women planning to undergo cancer therapy and other treatments.

IN THIS ARTICLE

When and how to evaluate patients complaining of infertility

Infertility is a disease, but there are different opinions about when a woman reporting this condition should be assessed (**TABLE 1**). According to the ASRM, a couple should not be considered infertile until they have tried to conceive spontaneously for at least 12 months, unless the medical history and physical findings dictate earlier evaluation and treatment.[1]

For example, approximately 25% of couples experience infertility when the woman is age 35, and about 50% experience it when the woman is age 40. Therefore, it is reasonable to investigate infertility after 6 months of attempted conception when the woman is over 35 and after 3 months if she is over age 40.[2] The primary reason for this age-related reduction in fertility is the diminishing number and quality of oocytes over time.

Other risk factors for infertility include smoking, family history of premature ovarian failure, significant ovarian pathology, previous ovarian surgery, history of oligomenorrhea or amenorrhea, known or suspected disease of the uterus or fallopian tubes, endometriosis, or a partner known to be subfertile.[3,4]

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TABLE 1

When to investigate infertility, treat, and refer

INVESTIGATE
After 12 months of unprotected intercourse if age <35
After 6 months of unprotected intercourse if age 35–39
After 3 months of unprotected intercourse if age ≥40
After 0–6 months if patient has history of or risk factors for infertility
TREAT
Treat identifiable causes of infertility
Optimize factors influencing fertility:
• Diet, weight, exercise
• Timed intercourse
Treat empirically (eg, clomiphene, insemination) for 3–6 months in patients <40
REFER
History of infertility or significant risk factors
Significant fertility problems identified during investigation
Age ≥40
After 3–6 months of failed treatment for identifiable causes
After 3–6 months of failed empiric treatment

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Failure to achieve pregnancy after 3 to 6 cycles of ovarian stimulation signals the need to expand evaluation or change treatment strategies

How to evaluate ovarian function

A careful history and physical examination are key components of systematic, expeditious, and cost-effective identification of the cause of infertility (**TABLE 2**). A menstrual history and basal body temperature recordings are useful in the diagnosis of ovulatory dysfunction and are easy to obtain. Measurements of urinary luteinizing hormone (LH) using ovulation-prediction kits and mid-luteal-phase serum progesterone are also helpful.

Endometrial biopsy is rarely indicated because of its lack of clinical relevance.

Serial vaginal ultrasonography of the size and number of ovarian follicles may be indicated when simpler methods are inconclusive.

Other tests to evaluate ovarian function may include thyroid-stimulating hormone (TSH), serum prolactin, cycle day 3 follicle-stimulating hormone (FSH) and estradiol, and the clomiphene citrate challenge test in selected patients at higher risk of ovarian dysfunction.

Clomiphene citrate is preferred

Ovarian dysfunction can be treated with clomiphene for 3 to 6 cycles[5] starting at 50 mg per day from cycle day 5 to 9 and increasing to 100 and then 150 mg per day if ovulation does not occur. The drug may also be effective empiric treatment for unexplained infertility using 100 mg per day from cycle days 3 through 7 for a maximum of 3 to 4 cycles.

Only gynecologists experienced with ovarian stimulation drugs and with access to daily ultrasonographic monitoring and estradiol levels should use them, because of the risk of multiple pregnancy and ovarian hyperstimulation.

For women with polycystic ovary syndrome (PCOS), clomiphene alone is more effective than metformin alone. Ovarian drilling may be an effective surgical treatment for PCOS if clomiphene fails, but the cost and risk of adhesions must be considered.

Human chorionic gonadotropin (hCG) injections during clomiphene treatment to stimulate ovulation should be given only if the patient's own urinary LH surge cannot be detected.

A single intrauterine insemination (IUI) improves the pregnancy rate slightly in conjunction with clomiphene, and by an odds ratio of approximately 2 in conjunction with gonadotropins. The gonadotropin dosage ranges from about 75 to 600 IU per day for 8 to 12 days, based on patient need and careful monitoring.

When to give up on ovarian stimulation. Failure to achieve pregnancy after 3 to 6 cycles signals the need to expand diagnostic evaluation or change treatment strategies.

Evaluate the uterus and tubes

Uterine factors rarely cause infertility but warrant thorough investigation all the same, including assessment of uterine cavity size and shape. A number of methods are available:

- hysterosalpingography (HSG)
- ultrasonography
- saline sonohysterography

Tubal factors can be evaluated using HSG or laparoscopy with "chromotubation." Fluoroscopic or hysteroscopic selective tubal cannulation confirms or

excludes any proximal tubal occlusion suggested by HSG or laparoscopy and may help correct it via recanalization using specialized catheter systems.

Peritoneal factors such as endometriosis or pelvic or adnexal adhesions may occasionally be identified by ultrasonography if there is a mass, but are more likely to require laparoscopy.

When laparoscopy is indicated

If there is evidence or a strong suspicion of endometriosis, pelvic or adnexal adhesions, or significant tubal disease, laparoscopy is warranted. It also may be helpful in younger patients (eg, <35 years) and women with a shorter duration of infertility (eg, <3–4 years), and when there is a reasonably normal male factor.

Because they reduce pregnancy rates by 50%, hydrosalpinges should be removed or the fallopian tube should be ligated proximally before IVF. It also is important to consider the number of patients needed to treat by laparoscopy to obtain 1 additional pregnancy.

Only gynecologists with expertise should perform laparoscopy, because it is important to make the correct diagnosis and be capable of surgically treating conditions found during the surgery.

Skip the postcoital test, but keep the semen analysis

Abnormalities of the cervical mucus or sperm–mucus interaction rarely cause infertility. Therefore, the postcoital test has questionable predictive value and is probably only useful to confirm that the couple can have properly timed intercourse during the cycle.[3]

A male factor is solely responsible in about 20% of infertile couples and contributory in another 30% to 40%. For this reason, semen analysis is always warranted when the female is being evaluated for infertility.

Examination of the male partner should be performed by the gynecologist, or the male should be referred to a urologist interested in infertility.[6]

TABLE 2

Current status of tests and treatments

OLD, NOW RARELY INDICATED
Postcoital test
Endometrial biopsy
Antisperm antibodies testing
Intracervical insemination
Clomiphene for more than 3–6 cycles
Routine hCG injection to stimulate ovulation in clomiphene cycles
NEW AND HELPFUL
Clomiphene citrate challenge test in selected patients
Serial vaginal ultrasounds to evaluate response to ovarian stimulation
Saline sonohysterography
Preimplantation genetic diagnosis for single-gene defects
Embryo cryopreservation
Single-embryo transfer to reduce multiple pregnancy rates
NEW BUT STILL EXPERIMENTAL*
Preimplantation genetic screening for aneuploidy in older patients
Human lymphocyte antigen typing for recurrent pregnancy loss
Intravenous immunoglobulin for recurrent pregnancy loss
Ovarian tissue or oocyte cryopreservation for fertility preservation

* Should be performed only in clinical trials

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For recurrent pregnancy loss, best treatment is TLC

Recurrent pregnancy loss is challenging because it is so emotionally charged for the patient, the cause is often unclear, and we lack specific treatments. A methodical and empathetic approach is therefore recommended.

What the history can reveal

Many women with recurrent pregnancy loss will eventually have a live birth, but increasing numbers of miscarriages do predict a poorer overall chance of success, as does increasing age.

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Lifestyle factors rarely, if ever, cause recurrent pregnancy loss, but the following factors may increase the risk of miscarriage: obesity, high daily caffeine intake, alcohol consumption, use of nonsteroidal anti-inflammatory drugs, and social class and occupation. A previous diagnosis of or treatment for infertility also increases the risk of recurrent loss.

Smoking should be discouraged and healthy lifestyles should be promoted.[7]

Causes of recurrent pregnancy loss

Definite causal factors include chromosomal abnormalities, such as translocations, in approximately 5% of couples with 2 or more losses.

Probable factors include uterine abnormalities (both congenital abnormalities such as septate, and acquired defects such as adhesions and intrauterine or submucous myomas), uncontrolled thyroid disease or diabetes, PCOS, and antiphospholipid antibody syndrome.

Other thrombophilias, such as those associated with factor V Leiden mutation, activated protein C resistance, and possibly prothrombin G20210A and protein S deficiency, have been found by some investigators to be associated with recurrent pregnancy loss. It is doubtful that antithyroid antibodies and sharing of parental human lymphocyte antigen (HLA) cause recurrent miscarriage.[7]

Genetic component likely. The risk of recurrent pregnancy loss in first-degree relatives of women with unexplained repeated pregnancy loss who have normal chromosomes is approximately 6 times higher than the risk in the background population, suggesting a polygenic mode of inheritance.[7,8]

Other possible causes include low plasma folate levels, which have been associated with an increased risk of first-trimester pregnancy loss. Environmental toxins such as ionizing radiation, organic solvents, alcohol, mercury, and lead are confirmed causes of recurrent pregnancy loss; hyperthermia is a suspected cause.[8]

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A previous diagnosis or treatment for infertility increases the risk of recurrent pregnancy loss

Recommended evaluation

Investigations that have been proven in many studies include:

- HSG, hysteroscopy, and sonohysterography
- karyotyping of the couple
- measurement of thyroid hormone
- hemoglobin A1C and serum glucose assessment
- activated partial thromboplastin time, dilute Russell viper venom time, and lupus anticoagulant assessment
- measurement of immunoglobulin G and immunoglobulin M anticardiolipin antibodies
- test for factor V Leiden mutation

Tests that are possibly useful include assessment of androgens and FSH in women with irregular periods.[7]

Examine products of conception?

Although it is routine practice to send products of conception for histologic examination, mainly to exclude a gestational trophoblastic disorder, the usefulness of this practice is unclear.[8] In couples with recurrent pregnancy loss, chromosomal analysis of the products of conception indicates that a normal conceptus karyotype in a previous pregnancy is a predictor of a higher rate of miscarriage in a subsequent pregnancy.[8] When stratified by maternal age, there is no difference in the distribution of cytogenetically abnormal miscarriages in couples with recurrent pregnancy loss, compared with controls.[8] The cost-effectiveness of karyotyping is therefore unclear.

High levels of homocysteine (ie, hyperhomocysteinemia) can be associated with recurrent pregnancy loss. Among genetic causes is polymorphism at position 677 in the methylene tetrahydrofolate reductase (MTHFR) gene, which is often evaluated to rule out this condition.

Infections with bacteria, viruses, or parasites can all interfere with early pregnancy development, but none seem to be a significant cause of recurrent pregnancy loss.[8] Testing is most useful in the context of an acute infectious episode.

Can recurrent loss be treated?

The hallmark of treatment is empathetic care, along with counseling emphasizing the complexity of this condition. Any endocrinologic, anatomic, or other abnormality that is identified during evaluation should be treated, if possible.

Progesterone supplementation is not proven treatment. This therapy is commonly prescribed but has not been proved to improve live birth rates.

Prednisone, aspirin, and NSAIDs have no benefits but potential risks and should not be used.

Current immunologic therapies for recurrent pregnancy loss have no sound scientific basis, except for the use of heparin and aspirin in patients with well-documented antiphospholipid antibodies.[7] Specifically, intravenous immunoglobulin remains unproven, is experimental, and should be provided only in approved research settings.[9] Paternal leukocyte immunization does not work, has been proscribed by the US Food and Drug Administration, and should be avoided.

Careful counseling and education of the patient about the history, pathophysiology, testing, test results, and treatment of recurrent pregnancy loss are necessary. Women with subfertility who have taken a long time to conceive should be treated empirically with ovarian stimulation in an attempt to shorten the time to conception.

Singleton births can be encouraged without jeopardizing IVF, ART

Multiple gestations have increased over the past 15 years, largely because of:

- ovulation induction for management of oligo-ovulation
- superovulation to produce more than 1 ovulated egg for fertility treatments
- assisted reproductive technologies (ART), in which more than 1 embryo is replaced to increase the pregnancy rate

Approximately 40% of triplet and higher-order pregnancies have resulted from ovulation induction and superovulation; 40% result from ART; and 20% occur spontaneously.[10] Variables that increase the risk of higher-order pregnancies include the infertile couple's sense of urgency, competitive pressures among IVF clinics, and inadequate or absent health-care insurance.

Multiple gestations are a bad idea

Risks include a higher complication rate for gravidas and fetuses, as well as higher short- and long-term costs to patients and society. It is therefore important to reduce the incidence of multiple gestation associated with fertility treatments.[10]

How to reduce the likelihood of multiple fetuses

- Closely monitor cycles involving ovulation induction and superovulation for efficacy and safety, to avoid ovarian hyperstimulation and reduce the risk of multiple gestation. Although attempts to limit multiple gestation during ovulation induction or superovulation using ultrasonographic criteria and serum estradiol limits have been ineffective,[10] it is my opinion that we should err on the side of conservatism, even though the optimal parameters for doing so have not been determined by high-quality trials. I recommend that hCG or IUI be avoided if more than 4 mature follicles (>15 mm) or 6 large follicles (>12 mm) are present on a sonogram, and the couple should be instructed to refrain from intercourse.
- Focus on the objective of a single healthy baby as the optimal outcome. Data published by the Society for Assisted Reproductive Technology (SART) clearly demonstrate the clinical impact of a reduction in the number

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Avoid hCG and intrauterine insemination if ultrasonography reveals more than 4 mature follicles (>15 mm) or 6 large follicles (>12 mm)

of embryos transferred, which reduced triplet pregnancy rates in 2005 to less than half the rate in the late 1990s. Fewer embryos are transferred today than just a few years ago, and the trend is continuing. This will help reduce the triplet rate further and also reduce twin pregnancies. In the past 6 months, guidelines have recommended replacement of only 1 blastocyst at day 5 or 1 to 2 embryos at day 3 in women under age 35 with a favorable prognosis.

What the future holds

We can expect more elective single-embryo or single-blastocyst transfers as we gain further expertise in this area. However, this practice should be implemented carefully in selected patients to maintain adequate pregnancy rates while reducing multiple gestations.

The United States has the highest ART success rates in the world (approximately 40% higher than in Europe) despite a reduction in the number of triplet or higher-order pregnancies resulting in live births after ART—from 7.0% in 1996 to 2.4% in 2004. The twin rate has remained stable at approximately 30%, but should decrease as 1- and 2-embryo transfers become more common.[11]

Preimplantation genetic diagnosis now has multiple applications

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Preimplantation genetic diagnosis has been performed broadly to diagnose Tay-Sachs, Huntington's disease, and other diseases that involve a single gene defect

Preimplantation genetic diagnosis (PGD) is over 15 years old, and at least 1,000 babies worldwide have been born after its use, with no reports of increased fetal malformation or other problems.[12]

Two basic techniques are employed to analyze the genomic status of the 1 or 2 blastomeres usually removed from the 8-cell embryo on day 3 after fertilization:

- **Polymerase chain reaction** (PCR) is used to amplify a specific DNA sequence harboring a mutation. A mismatch (eg, due to a genetic deletion) leads to differential migration on the gel, thus permitting diagnosis. The error rate, primarily due to allelic dropout, in which 1 of the 2 alleles selectively amplifies and thus contributes to diagnostic errors, is approximately 0.3% to 5.6%.
- **Fluorescent in situ hybridization** (FISH) allows determination of the ploidy of a blastomere. Labeled probes bind to chromosomes and are viewed under a fluorescent microscope. The error rate is 1% to 10% for a variety of technical reasons.[12] Testing takes about 1 day while the embryos are developing to blastocysts, at which time those that are viable and tested to be normal are transferred back into the uterus.

Not just for gender determination

PGD initially was used to determine gender (by FISH) as an indirect method of avoiding X-linked genetic diseases such as hemophilia. The error rate for gender determination is less than 1%. Since then, single-gene-defect disorders have been diagnosed using PCR and heteroduplex formation or restriction endonuclease digestion, both of which distinguish normal from mutant alleles. PGD has been performed broadly to diagnose Tay-Sachs, Huntington's disease, and hundreds of other diseases.

Testing for translocation by PGD has been especially useful and may reduce the risk of spontaneous abortion from as much as 95% to 13% if one of the parents is a known translocation carrier.

Still under investigation is the routine use of FISH to detect aneuploidy in cases of recurrent pregnancy loss. The use of FISH for gender selection for family balancing is not recommended by the ASRM.

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More young women seek to preserve their fertility

Fertility preservation through ovarian tissue or oocyte cryopreservation or vitrification has recently been popularized by cancer survival consumer groups, the media, and other interests. In addition to cancer patients planning to undergo chemotherapy or radiotherapy, candidates for fertility preservation include women undergoing bone marrow or stem cell transplantation or oophorectomy (for a benign tumor, endometriosis, or prophylaxis) and patients with severe autoimmune disease needing chemotherapy.

In cancer patients, fertility is preserved using one of several methods:

- **shielding or moving the ovaries** to a different anatomic site during radiation
- **use of gonadotropin-releasing hormone analogs** or oral contraceptives during chemotherapy (unproven)
- **changes** to chemotherapy regimen
- **IVF cycle followed by cryopreservation of embryos** if the patient has a male partner or is prepared to use donor sperm (provided the oncologist confirms that ovarian stimulation and high estradiol levels are acceptable and there is time to undergo an IVF cycle before cancer treatment begins).

Unresolved issues

Concerns about cryopreservation of ovarian tissue in cancer patients[13,14] include the possibility of reseeding tumor cells after ovarian transplantation, malignant transformation of transplanted ovarian tissue, and the possibility of congenital abnormalities as a result of cryopreservation—although no increase has been found in the patients studied so far.

The pregnancy rate is low

For cancer patients, the preservation of ovarian tissue or oocytes yields pregnancy rates significantly lower than those observed with standard IVF procedures. For cancer patients facing chemotherapy, however, oocyte cryopreservation may be one of the few options available and is acceptable in experimental protocols approved by the institutional review board.

Physicians should inform cancer patients about the options for fertility preservation prior to treatment.[14] We lack data to recommend ovarian tissue or oocyte cryopreservation for the sole purpose of circumventing reproductive aging in healthy women.[13] ■

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For cancer patients, the preservation of ovarian tissue or oocytes yields pregnancy rates significantly lower than those observed with standard IVF

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