FERTILITY

Here is new information on reducing adhesions, the stress and cost of fertility treatment, unhelpful testing, and "long-shot" oocyte cryopreservation

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The field of reproductive endocrinology and infertility is anything but stagnant. New technologies continue to enter the market at a brisk pace, and a greater emphasis on evidence has produced better-designed randomized controlled trials, meta-analyses, and practice guidelines. This means greater availability of standardized protocols that reflect best practice and can be tailored to a patient's condition and needs.

Highlighted here are notable studies and guidelines from the past year, including advice on:

- preventing peritoneal adhesions
- expediting in vitro fertilization (IVF) for unexplained infertility
- counseling the patient about the real limitations of preimplantation genetic screening for aneuploidy
- informing patients that oocyte cryopreservation is unlikely to lead to live birth.

IN THIS ARTICLE

Guideline urges good surgical technique in battle against adhesions

Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society of Reproductive Surgeons. Pathogenesis, consequences, and control of peritoneal adhesions in gynecologic surgery. Fertil Steril. 2007;88:21–26.

This newly released practice guideline from the American Society of Reproductive Medicine (ASRM) focuses on adhesions and their impact on fertility. The guideline reiterates that peritoneal adhesions are a common and serious complication of gynecologic surgery and emphasizes key principles to reduce their likelihood and extent. These principles include the need to:

- Perform surgery only when the benefits of doing so clearly outweigh the risks
- Handle tissue gently (this is the most important preventive technique)
- Don't assume laparoscopy is superior to laparotomy—it will be only if less tissue injury occurs
- Be especially careful when operating on or near ovaries, which form adhesions easily.

Ovarian surgery often necessitates additional operations

Studies have demonstrated that approximately 33% of patients who undergo open abdominal or pelvic surgery are readmitted, on average, two times over the subsequent 10 years for conditions directly or possibly related to adhesions or for further surgery that could be complicated by adhesions. The highest readmission rate directly related to adhesions—7.5 for every 100 initial operations—was associated with ovarian surgery performed via laparotomy.

Adhesion-related complications of gynecologic surgery include small-bowel obstruction, which occurs in approximately 1.5% of women who have undergone abdominal hysterectomy.

The relationship between adhesions and pelvic pain is unclear, although severe bowel adhesions can cause visceral pain. The ASRM guideline notes that "the impact that lysis of bowel or adnexal adhesions may have on abdominal and pelvic pain cannot be predicted confidently." Postoperative adhesions increase subsequent operating times and risk of bowel injury.

How adhesions affect fertility

Adhesions may impair fertility by distorting adnexal anatomy and interfering with gamete and embryo transport. Among infertile women who have adnexal adhesions, adhesiolysis is associated with pregnancy rates of 32% at 12 months and 45% at 24 months, compared with 11% and 16%, respectively, for untreated women.[1] Pregnancy rates are inversely correlated with adhesion scores on the ASRM classification system for adnexal adhesions.[2]

Some, but not all, adhesion-reducing measures work

According to the ASRM guideline, adhesions may be prevented, at least theoretically, by:

- minimizing peritoneal injury during surgery
- avoiding the introduction of reactive foreign bodies
- reducing the local inflammatory response
- inhibiting the coagulation cascade and promoting fibrinolysis
- placing barriers between damaged tissues.

Pharmacotherapeutic and fluid agents. ASRM found no evidence of improved pregnancy outcomes for pharmacologic and fluid agents used as an adjunct during pelvic surgery. For example, anti-inflammatory agents that have been evaluated, both locally and systemically, including dexamethasone and promethazine, have not reduced postoperative adhesions. Antibiotic solutions, 32% Dextran 70, and crystalloid solutions such as normal saline and Ringer's lactate with or without heparin or corticosteroids have been used to separate adjacent peritoneal surfaces via "hydroflotation," but none have reduced adhesion formation.

Surgical barriers may help decrease postoperative adhesion formation but cannot compensate for poor surgical technique. I rarely use adhesion barriers because I feel that careful tissue handling, excellent hemostasis, avoiding trauma to healthy tissue, and removal of all diseased tissue are the key ways to obtain good postsurgical results and reduce adhesions.

Hyaluronic acid agents may decrease the prevalence of adhesions and prevent the deterioration of preexisting adhesions, but because of the limited number of studies available, these data should be interpreted with caution.[3] However, ASRM found no substantial evidence that they improve fertility, decrease pain, or reduce the incidence of postoperative bowel obstruction.

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***FAST** TRACK*

Careful tissue handling, excellent hemostasis, avoiding trauma to healthy tissue, and removing all diseased tissue are the key ways to reduce adhesions

More ONLINE
For more on the prevention of adhesions, see our May 2007 issue

Averting adhesions: Surgical techniques and tools
By Togas Tulandi, MD, MHCM, and Mohammed Al-Sunaidi, MD
It's available in our archive at www.obgmanagement.com

A move from clomiphene directly to IVF may cut time to pregnancy

Reindollar RH, Regan MM, Neumann PJ, Thornton KL, Alper MM, Goldman MB. A randomized controlled trial of 503 couples assigned to conventional infertility treatment or an accelerated track to IVF: Preliminary results of the fast track and standard treatment (FASTT) trial. Fertil Steril. 2007;88(Suppl 1):S41.

This very important abstract, presented at the annual meeting of ASRM, has the potential to dramatically change fertility treatment. The multicenter randomized controlled clinical trial measured the efficacy and time to pregnancy of an accelerated treatment strategy for women 21 to 39 years old who had unexplained infertility. A similar percentage of patients—approximately 75%—became pregnant in each arm (traditional versus accelerated), with a shorter time to pregnancy in the accelerated arm.

The new paradigm for management of unexplained infertility includes:

- comprehensive fertility history and physical examination
- targeted laboratory testing and other investigation, as needed
- counseling and psychological support for the patient once the diagnosis is made
- empiric treatment with clomiphene citrate plus intrauterine insemination (IUI) for as many as three cycles
- immediate IVF for as many as six cycles.

***FAST** TRACK*

Avoiding the use of gonadotropins and moving straight to IVF reduces the risk of multiple pregnancy

Details of the trial

Women in the trial had attempted to conceive for 12 months and had normal ovarian reserve (and semen analysis) and no pelvic pathology. Couples already treated for infertility were excluded.

Participants were randomized to:

- a conventional treatment regimen of three cycles of clomiphene citrate with IUI, three cycles of follicle-stimulating hormone (FSH) and IUI, and as many as six cycles of IVF or
- three cycles of clomiphene citrate with IUI and then as many as six cycles of IVF.

Time to pregnancy was defined as the time from randomization to confirmation of a fetal heart beat for a delivery resulting in a live birth. The trial was stratified by age (younger than 35 years versus 35 or older), recent laparoscopy (yes/no), and study site.

Regimen likely reduces cost, stress

Major issues affecting the eventual success rate for infertile couples are cost and psychological stress, which can cause even patients who have a good prognosis to drop out of treatment. The major complication of fertility treatment is multiple pregnancy. By avoiding the use of gonadotropins in couples with unexplained infertility and accelerating the transition to IVF, physicians can lower the cost and psychological stress of treatment. They can also reduce the likelihood of multiple pregnancy because it is easier to control the number of embryos transferred in IVF than the number of follicles that develop with gonadotropins.

In women younger than 35 years on the first IVF cycle who have a good prognosis, ASRM now recommends that only one or two day-3 embryos be transferred, and not more than one day-5 blastocyst.[4] The multiple-birth rate has declined in recent years, as more and more IVF clinics place fewer embryos; the rate should continue to fall with wider application of elective single-embryo transfer.[5,6]

Because this accelerated protocol produces a similar number of births over a shorter period and has the potential to lower cost, psychological stress, and the multiple-birth rate, it deserves implementation for many patients and warrants further evaluation for potential benefits in other populations.

CONTINUED

It's no help, after all: Preimplantation genetic screening for aneuploidy

Practice Committee of the Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine. Preimplantation genetic testing: A Practice Committee report. Fertil Steril. 2007;88:1497–1504.

Mastenbroek S, Twisk M, van Echten-Arends J, et al. In vitro fertilization with preimplantation genetic screening. N Engl J Med. 2007;357:9–17.

Preimplantation genetic diagnosis of known single-gene defects, structural chromosomal rearrangements, X-linked disorders, and human leukocyte antigen typing is a major benefit to couples known to be at risk of passing on a heritable and debilitating genetic disease. Aneuploidy is the most common cause of early pregnancy loss, and its prevalence increases with maternal age and may increase in chromosomally normal couples who experience recurrent early pregnancy loss or repeated failure of IVF cycles. Preimplantation genetic screening (PGS) has been advocated to identify and transfer only euploid embryos and increase the chance of successful pregnancy.

New data from Mastenbroek and colleagues indicate that PGS for aneuploidy does not increase the rate of pregnancy or live birth. After several years of increasing utilization and studies suggesting that PGS has benefit, the first multicenter, randomized, double-blind, controlled study that compared three cycles of IVF with and without PGS in women 35 to 41 years old concluded that PGS does not increase but, in fact, significantly reduces the rate of pregnancy and live birth in this group.

Findings sparked controversy

This trial generated controversy within the genetics and reproductive endocrinology specialties because it challenged the intuitive view that screening of embryos before transfer into the uterus should be beneficial—or, at least, harmless. Some now argue that the benefits of PGS, if any, cannot be intuitively assumed and assert that the burden of proof of those benefits rests with proponents of PGS.

The practice committees of the Society for Assisted Reproductive Technology (SART) and ASRM found insufficient evidence to support the use of PGS to improve the live birth rate in women of advanced age or in those who have had implantation failure or recurrent pregnancy loss (**TABLE**). Many physicians believe, however, that technologies under development will soon bring verifiable benefits of PGS to patients.

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SART and ASRM weigh in on use of preimplantation genetic testing

TEST	RECOMMENDATION
Preimplantation genetic diagnosis	• Provide genetic counseling to help the patient understand: - risk of having an affected child - impact of the disease - limitations of options that may help prevent the birth of an affected child • If one or both parents carry a genetic abnormality, the risk of conceiving a child with the same abnormality can be identified with tests performed on a single cell • Prenatal diagnostic testing to confirm the results of preimplantation genetic diagnosis is strongly encouraged because of the possibility of a false-negative result
Preimplantation genetic screening	• Provide thorough education and counseling to the patient before preimplantation genetic screening is performed, including explanation of: - its limitations - risk of error - lack of evidence that it improves pregnancy rates • Evidence does not support the use of preimplantation genetic screening as currently performed to improve live birth rates in patients with: - advanced maternal age - previous implantation failure - recurrent pregnancy loss

SOURCE: Society for Assisted Reproductive Technology and American Society for Reproductive Medicine

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Advise your patients that oocyte cryopreservation is "a long shot"

Practice Committee of the Society for Assisted Reproductive Technology and Practice Committee of the American Society for Reproductive Medicine. Essential elements of informed consent for elective oocyte cryopreservation: a practice committee opinion. Fertil Steril. 2007;88:1495–1496.

Oocyte cryopreservation is an experimental procedure that should not be offered or marketed as a means to defer reproductive aging, primarily because data on clinical outcomes are limited. That is the conclusion of this guideline from SART and ASRM. Consequently, women who may be considering the procedure should be fully informed about the process and likely outcomes and counseled by a qualified mental health professional.

Counseling is crucial

According to the SART and ASRM guideline, pretreatment counseling should include comprehensive information on a range of topics (see the box below). In addition, women considering oocyte cryopreservation should be counseled thoroughly about reproductive aging and life planning.[7,8]

Few alternatives for some women

Women who have cancer should receive the same counseling. Unlike healthy women, however, they may have no other options, and cryopreservation may be more appropriate for them despite experimental status. ■

Be forthright about oocyte cryopreservation

Patients considering this procedure need comprehensive information about:

- Ovarian stimulation and oocyte retrieval
- Methods of oocyte cryopreservation
- Storage fees
- The expected thaw survival rate
- The requirement for intracytoplasmic sperm injection
- Clinic-specific data and outcomes or, in their absence, literature estimates of a 2% overall live birth rate per oocyte thawed using slow-freeze methods and 4% for vitrification, compared with age-related probabilities of success per IVF cycle using fresh nondonor oocytes
- The relatively low likelihood that a woman who cryopreserves her eggs before age 35 will ever need or use them
- Disposition of any cryopreserved eggs not used by a predetermined age
- State and federal screening laws for potential donation of cryopreserved oocytes
- Potential risks of basing important life decisions and expectations on a limited number of cryopreserved oocytes
- The possibility that the facility may cease operation, necessitating transfer of cryopreserved oocytes to another facility
- The possibility that cryopreserved oocytes might be lost or damaged as a result of laboratory error or other events beyond control.

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