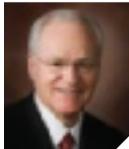




FERTILITY

If you're looking for better ways to treat infertility or enhance fecundity, here are some developments you'll want to know about



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The diagnosis and treatment of fertility are evolving rapidly as a result of clinical studies, scientific research, and changing socioeconomic and ethical perspectives. These developments benefit health-care consumers, but they also pose new challenges to general ObGyns and other practitioners committed to the best possible care for their patients.

In this Update, I focus on a number of these areas of change:

- care of women who have polycystic ovary syndrome (PCOS)
- the impact of myomas on fertility
- treatment of infertility in women who have endometriosis
- when tubal reconstruction is appropriate
- the impact of a woman's age on fertility
- patient-friendly strategies to enhance fertility
- cross-border reproductive travel.

Use clomiphene citrate to stimulate ovulation in women who have PCOS

Practice Committee of the American Society for Reproductive Medicine. Use of insulin-sensitizing agents in the treatment of polycystic ovary syndrome. Fertil Steril. 2008;90(5 Suppl):S69-S73.

A new Committee Opinion from the American Society for Reproductive Medicine (ASRM) Practice Committee tackles the challenge of treating women with PCOS for infertility.

PCOS is associated with an increased risk of insulin resistance and diabetes mellitus. The first line of treatment for all women who have PCOS, especially those with an elevated body mass index, is **lifestyle modification through diet and exercise**, with the goal of losing weight.

Clomiphene is first-line therapy when ovulation is the aim

Metformin and other insulin-sensitizing agents may enhance ovulation and increase the response to clomiphene citrate in women who have PCOS and insulin resistance, but their use solely to enhance ovulation is unwarranted, and they do not reduce the rate of miscarriage. Clomiphene citrate should be the first-line treatment because it is much more effective. Long-term use of metformin to prevent disease is not advised.

Screen for insulin resistance at the time of diagnosis

Women who have PCOS should be given a

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5-STEP TREATMENT OF ANOVULATORY INFERTILITY FOR WOMEN WHO HAVE PCOS

My strategy for stimulating ovulation in this population involves the following:

1. Perform **vaginal ultrasonography (US)** on cycle day 3 for an antral follicle count and to rule out ovarian cysts >1 cm.
2. Give **clomiphene citrate**, 50 mg, on cycle days 3 through 7 (or 5 through 9).
3. **Repeat vaginal US** on cycle day 11 (or 13) to evaluate ovarian response. The optimal response is 1 to 2, and not more than 3, follicles ≥ 15 mm in size.
4. Recommend **timed intercourse**, starting on cycle day 10 and then every 2 ± 0.5

days until 1 to 2 days after ovulation.

5. **Measure urinary luteinizing hormone (uLH)** daily, to detect uLH surge, starting on cycle day 11. A positive surge indicates that ovulation is likely within the next 12–48 hours. Absence of a surge indicates the likely absence of ovulation, which can be treated by giving 10,000 IU of human chorionic gonadotropin (hCG) subcutaneously or intramuscularly when the largest follicle is 18 to 25 mm in size.

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2-hour oral glucose tolerance test and have their lipid profile measured at the time of diagnosis and then at an interval of every 2 years. Insulin-sensitizing agents should be

used for long-term health issues only after impaired glucose tolerance has been measured, if diet and exercise alone prove to be ineffective.

FAST TRACK

Postoperative adhesions after abdominal myomectomy may reduce fertility

When choosing a treatment for myoma, consider impacts on fertility

Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society of Reproduction Surgeons. Myomas and reproductive function. Fertil Steril. 2008;90(5 Suppl): S125-S130.

A recent educational bulletin from the ASRM Practice Committee examined the relationship between myomas and reproductive function and reviewed management of this pathology.

The effects of myomas on reproductive outcome are ill-defined, but fibroids that distort the uterine cavity, as well as larger intramural myomas, may have adverse effects on fertility.

Select interventions carefully

Among women who have infertility and those who have recurrent pregnancy loss,

myomectomy should be considered only after thorough evaluation. The reason? Postoperative adhesions as a result of abdominal myomectomy are common and may reduce subsequent fertility.

As for uterine artery embolization, myolysis, and MRI-guided ultrasonic treatment, these are not recommended for women who have myomas and who are seeking to maintain or improve fertility. The safety and efficacy of these procedures in this population have not been established.

Is a GnRH agonist useful?

Treatment of myomas with a gonadotropin-releasing hormone (GnRH) agonist does not improve fertility but may be helpful before surgery in anemic women and in those who might be able to undergo a less invasive procedure if the myoma volume were moderately smaller.

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Sequence of infertility treatments is critical in endometriosis patients

Adamson G. Management of endometriosis and infertility following surgery. In: Sutton C, Jones K, Adamson GD, eds. Modern Management of Endometriosis. London: Taylor & Francis; 2006:273-287.

New data make it easier to treat infertility in women thought to have endometriosis, although further randomized trials are needed. If other fertility variables are normal, and minimal to mild endometriosis is suspected but not confirmed, clomiphene citrate, 100 mg on cycle days 3 through 7, followed by intrauterine insemination (IUI) for 3 to 6 cycles, is a reasonable initial treatment, with the higher number of cycles being reserved for younger patients and those who have a better prognosis.

When is surgery helpful?

Diagnostic or operative laparoscopy, or both, is often indicated when one or more of the following are present:

- The patient experiences pain
- She fails to conceive after clomiphene citrate is administered and IUI is attempted for 3 to 6 cycles
- She has other factors associated with infertility.

If it is well performed, surgery is effective treatment for all stages of endometriosis, endometriomas, and disease of the cul de sac, for symptoms of pain or infertility, or both.

Generally, if pregnancy does not occur within 9 to 15 months after surgery, repeat surgery is of limited benefit for infertility, but

may have some benefit for pain. In women who do not conceive after surgery, ovarian suppression for 2 months is of possible benefit before assisted reproductive technology (ART) and should be considered in patients who are also suffering from pain. Pre-ART surgery for large endometriomas is frequently indicated, and excision of the cyst capsule produces results superior to those of drainage, coagulation, or both.

Postoperative management

After complete destruction of endometriosis in women who have infertility, ovarian suppression is not indicated. Rather, the patient should usually attempt to conceive for 9 to 15 months, with an outside range of 3 to 24 months for much older women who have an unfavorable prognosis, and for much younger women who have a good prognosis, respectively. If pregnancy does not occur, clomiphene citrate and IUI for 3 to 6 months are then indicated.

If this last strategy is unsuccessful, the options include:

- **gonadotropins and IUI** for 3 months to a maximum of 6 months in the young patient who has a good prognosis
- **repeat laparoscopy** (although this option is rare), possibly in conjunction with **gamete intrafallopian transfer** (GIFT), or, alternatively, **in vitro fertilization** (IVF). If the patient had a technically inadequate operation the first time, it sometimes is appropriate to repeat the surgery or go directly to IVF.



Well-performed surgery is effective for all stages of endometriosis, endometriomas, and disease of the cul de sac, to treat pain or infertility, or both

Consider tubal reconstruction in carefully selected patients

Practice Committee of the American Society for Reproductive Medicine. The role of tubal reconstructive surgery in the era of assisted reproductive technologies. Fertil Steril. 2008;90(5 Suppl):S250-S253.

In the era of ART, tubal reconstruction has fewer indications but is still appropriate and effective in properly selected individuals.

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Determine the extent of tubal disease before reconstructive surgery

Hysterosalpingography is a useful initial test for the evaluation of tubal patency, but laparoscopy often is necessary to identify the nature and extent of pelvic disease. Selective salpingography or hysteroscopic tubal recanalization can help confirm the diagnosis of true proximal tubal occlusion.

Advise the patient of risks of surgery

Generally, the risk of ectopic pregnancy after tubal reconstruction is comparable to the risk of ectopic pregnancy associated with IVF, but the extent of tubal disease and pelvic pathology are important variables in predicting intrauterine and ectopic pregnancy rates.

The pregnancy rate after reversal of tubal sterilization depends on **1)** the type of sterilization procedure that was performed, **2)** site of anastomosis, and **3)** postoperative tubal length, as well as **4)** sperm quality and **5)** the age of the female patient.

Maternal age, number of children desired, coexisting infertility variables, risk of ectopic and multiple pregnancy, and treatment cost are important considerations when counseling patients about the relative advantages and disadvantages of tubal surgery and IVF.

IVF is the best treatment for older women of reproductive age who have significant tubal pathology, and for women who have both proximal and distal occlusion.

Age, and duration of infertility, are key determinants of treatment

Committee on Gynecologic Practice of the American College of Obstetricians and Gynecologists, and Practice Committee of the American Society for Reproductive Medicine. Age-related fertility decline: a Committee Opinion. Fertil Steril. 2008;90(5 Suppl):S154-S155.

Women older than 35 years should receive expedited evaluation and treatment for infertility if they have not conceived after 6 months, or earlier if clinically indicated. That's one of the conclusions from a recent ACOG-ASRM joint Committee Opinion on age-related fertility decline.

Age remains a major variable influencing a woman's fertility and risk of pregnancy loss, and is increasingly important because of the social trend toward deferred child-bearing. The fertility rate peaks in a woman's mid-20s and decreases by approximately 25% by age 35 and 50% by age 40, with a concomitant (and significant) increase in rates of aneuploidy and miscarriage.

The duration of infertility also is key. Of any given 100 women attempting to conceive:

- 78 will succeed within 1 year

- 88 will conceive within 2 years
- only an additional two or three women will conceive in the third year
- one more will conceive in each of the fourth and fifth years
- only three more will conceive over the rest of their reproductive life.

These data suggest that infertility should be investigated after 12 or more months of regular unprotected intercourse, with earlier evaluation and treatment for women who are older than 35 years.

Recurrent pregnancy loss and infertility are separate entities

By definition, recurrent pregnancy loss entails the loss of two or more pregnancies. When the cause is unknown, each loss merits careful review to determine whether specific evaluation may be appropriate. After three losses, thorough evaluation is warranted.^{1,2}

To distinguish infertility from recurrent pregnancy loss, define clinical pregnancy as one documented by US or histopathology.

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The fertility rate peaks in women's mid-20s and declines by about 25% by age 35 and 50% by age 40

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New technologies remain unproven

Although ovarian tissue and oocyte cryopreservation offer the promise of female fertility preservation, these technologies

remain investigational to date.

The greatest benefit to patients who wish to preserve their fertility is appropriate counseling about their reproductive health.^{3,4}

Fertility can be enhanced with a few patient-friendly strategies

Practice Committee of the American Society for Reproductive Medicine in collaboration with the Society for Reproductive Endocrinology and Infertility. Optimizing natural fertility. Fertil Steril. 2008;90(5 Suppl):S1-S6.

Another Committee Opinion from ASRM, in collaboration with the Society for Reproductive Endocrinology and Infertility, offers simple but effective steps for patients to take to optimize fertility. ObGyns should recommend these strategies to any woman planning to conceive in the near future.

Frequent intercourse is best

Intercourse every day or every other day yields the highest pregnancy rate, but intercourse two to three times a week is nearly equivalent. There is a “fertile window” that spans the 6-day interval ending on the day of ovulation, and it correlates with the volume and character of cervical mucus.

Among women who have regular menstrual cycles, frequent intercourse that begins soon after the cessation of menses can help maximize fecundity.

Devices that determine or predict the time of ovulation may be useful for couples who have infrequent intercourse.

Neither specific coital timing, nor position during coitus, nor rest in a supine position after intercourse has a significant impact on fertility.

Caffeine, alcohol OK—in moderation

Moderate caffeine or alcohol consumption (1 or 2 drinks daily) has no demonstrable adverse effect on fertility. Smoking, a higher

level of alcohol consumption (≥ 2 drinks daily), use of recreational drugs, and most commercially available vaginal lubricants should be discouraged among patients who are trying to conceive.

Fertility rates are lower in women who are very thin or obese, but there is little evidence that dietary variations improve fertility or affect the gender of the infant.

Elevated blood mercury levels from heavy seafood consumption have been associated with infertility.

Saunas do not reduce fertility in women. In normal men, attempts to protect the testicles from excessive heat are unjustified.

Avoid solvents and pesticides

- Fecundity may be diminished in women who are exposed to certain toxins and solvents, such as those used in the dry-cleaning and printing industries.
- Men who are exposed to heavy metals may be more likely to have abnormal semen parameters.
- Pesticide exposure may be a problem for both male and female agricultural workers.
- Despite limited data on exposure to lead and use of industrial microwaves, they are probably best avoided or minimized.
- Prescription drug use should be carefully controlled and managed on an individual basis.

Recommend 400 µg of folic acid daily

Any woman hoping to conceive should be advised to initiate this regimen to reduce the risk of neural tube defects.



Intercourse every day or every other day yields the highest pregnancy rate

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WHO AND CDC AGREE: INFERTILITY IS A COMMON PUBLIC HEALTH PROBLEM

The Centers for Disease Control and Prevention (CDC) held its first Public Health Symposium on Infertility in September 2008. Consensus is growing that infertility is a common disease or disability that has serious consequences for the well-being of families—making it a public health concern.

Because only approximately 50% of patients who have infertility ever seek treatment, it is hoped that new programs will improve access to fertility treatment for many more women.

For more information on the CDC's initiatives in reproductive health, visit: <http://www.cdc.gov/reproductivehealth/>

WHO focuses on international inequities
The World Health Organization (WHO) held

a meeting in Geneva in December 2008 to modify its glossary of ART definitions and develop new terminology to allow the collection of better data on the use of IVF internationally.^{5,6}

The prevalence of infertility is about the same in all countries of the world, affecting, on average, about 9% of people of reproductive age. However, there is a greater degree of secondary infertility—mostly as a result of infectious disease and obstetric complications—in low-resource (developing) countries.

Infertility is a major burden with serious medical and psychological consequences in American society, but its impact on women in other cultures is often more profound, with loss of personal status, divorce, and social ostracism adding to the burden.

More and more women seek care in countries other than their own

“Medical tourism” is an interesting phenomenon that has received widespread media attention. When it applies to infertility, a more appropriate term may be “cross-border reproductive care.”

This is an international phenomenon that is, so far, poorly documented. Common reasons to travel for medical care include cost and availability of specialized services. Women grappling with infertility may also seek to bypass regulations or ethical issues that limit

availability of treatment in their home country. Among the issues that prompt travel are:

- gamete and embryo donation
- payment of donors and surrogates
- nontraditional relationships.

The Canadian government hosted the first international symposium on cross-border reproductive care last month in an effort to learn more about this complex issue and identify ways to ensure the quality and safety of such services. 

FAST TRACK

Only approximately 50% of patients who have infertility ever seek treatment, often because they lack access to care

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