

Know When to Treat, When to Refer for Infertility

Patient age is perhaps the most important factor in choosing whether to go with treatment or referral.

BY BETSY BATES
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SAN FRANCISCO — Many young infertility patients can be worked up and started on a course of therapy without referral to a reproductive endocrinologist or fertility clinic, said Dr. Charles E. Miller at Perspectives in Women's Health, sponsored by OB.GYN. NEWS.

Others, however, deserve an immediate referral for in vitro fertilization, since their chances of pregnancy may be fading fast, said Dr. Miller, director of minimally invasive gynecologic surgery at Advocate Lutheran General Hospital, Park Ridge, Ill.

Patients to refer include all women over 40 years, patients with hypogonadotropic hypogonadism, tubal blockage, inadequate ovarian function, and those in whom simple treatments have failed, as well as males with severe semen deficiencies, including problems with sperm morphology.

In remaining couples, a simple work-up can be launched, but it should be done correctly, preventing the need for repeat examinations.

For example, a day 3 follicle-stimulating hormone (FSH) level below 10 mIU/L is an important marker of impaired ovarian reserve, but it should not be interpreted in isolation, said Dr. Miller.

Estrogen counts, too.

"If I see an FSH of 8 and an estradiol of 90, that looks every bit as abnormal to me as an FSH of 15 and an estradiol of 50," he said.

The age of the patient also provides context with regard to her FSH levels, which can fluctuate. Low FSH rates are less of a problem in women under 35, as are many signs of impaired fertility.

Even in vitro fertilization success rates decline precipitously in the mid- to late third decade.

"At my lab we do very, very well until

age 37 and there is a dramatic decline. If you look at most peoples' results in the good clinics around the U.S. at the present time, by 37 things get to be a little bit funky," he said.

A basic work-up begins by taking a focused history, including a history of surgical or medical events, illnesses such as thyroid disease or diabetes, sexual development, use of birth control, previous pregnancies, current health status, and sexual practices.

Tests and examinations concentrate on exploring potential ovulatory dysfunction/failure, tubal uterine or peritoneal abnormalities, or cervical, immunologic, or infectious contributors to why a couple has been unable to get pregnant for a year (6 months in a woman over 35).

Both partners should be asked about possible lifestyle contributors, including substance use, said Dr. Miller.

"You have to talk to your patients about this. If a male is doing marijuana three or four times a week, that is not going to be helping his sperm, I can assure you," he said. Even cigarette smoking is a "real concern, so much so that when we do studies ... we exclude women who smoke."

Among infertility tests and procedures that may be performed by general ob.gyn. and family physicians:

► **Laboratory tests.** For day 3 of a woman's cycle, Dr. Miller orders an FSH, estrogen, luteinizing hormone (LH), thyroid-stimulating hormone (TSH), fasting prolactin.

► **Ultrasounds.** Obtain a baseline ultrasound to examine the follicles on day 3 of the cycle to assess the presence of small "resting" antral follicles less than 9 mm in

each ovary. Fewer than six total antral follicles (in both ovaries) is a predictor of poor outcome; these patients should be referred. Then have the patient start a urine ovulation predictor kit at midcycle (day 11 if the patient has a 28-day cycle, but day 13 if her cycle is 30 days). Immediately following a positive color change, have the patient come in for another ultrasound to assess follicle production. A mature follicle that contains a mature egg should be 15-20 mm. Look again at the patient's estrogen level, since a mature follicle may produce a serum estrogen of 200 pg/mL.

► **Ovulation induction.** Use oral medications or injections with the goal of establishing a normal ovulatory cycle for timing of intercourse or inseminations.

► **Male work-up.** This should include a physical examination,

laboratory tests (testosterone, TSH, prolactin, FSH, and LH). Sperm analysis should be calculated using a formula of volume (greater than 2.0 mL), concentration (greater than 20 million/mL), and motility (greater than 50% with forward progression), and morphology (greater than 30% normal forms). Considered together, fewer than 10 million total motile sperm is an indicator of a fecundity problem.

Furthermore, "morphology counts," said Dr. Miller. "Males with abnormal sperm morphology should be referred to a male infertility specialist."

► **Postcoital test.** Aspirate mucus from the surface of the cervix 2-6 hours after the couple has had intercourse at midcycle. A color change is seen just as in the ovulation predictor test. Primary care physicians still use this as a general screen to evaluate the viscosity of the mucus and the activity of the sperm, indicating that the patient should be referred if either is abnormal. (This test is generally not used by reproductive endocrinologists, who move directly on to insemination if there

is an indication of sperm dysfunction.)

► **Hysterosalpingogram.** Schedule the test for day 6-12 to assess the structure and patency of the fallopian tubes.

► **Midluteal serum progesterone levels.** Timing is everything with this test, said Dr. Miller. "I see clinic after clinic after clinic ... getting a day 21 progesterone [in a] patient with a 35-day cycle. You want to get that progesterone level a week after ovulation and a week prior to menstruation. Time it based on cycle length."

► **Clomiphene challenge test.** Draw a day 3 FSH and estradiol, and order clomiphene citrate, 100 mg daily on days 5-9. Draw FSH again on day 10. A poor prognosis is associated with either an abnormal day 3 FSH or day 10 FSH, or if the sum of the day 3 and day 10 FSH is less than 26.

► **Surgery.** Consider with caution performing minimally invasive surgery to correct anatomic problems, scarring, adhesions, endometriosis, or fibroids, although the cost of surgery and the potential advantages of in vitro fertilization should be considered.

► **Fertility drugs with insemination.** If the woman's follicles do not develop to a mature size or her estrogen or progesterone levels are low, Dr. Miller considers several courses of clomiphene citrate at low doses (50 mg for 5 days on days 3-7 or days 5-9.) Ovulation will occur in 80%-85% of women, and over four cycles, 40% of women will become pregnant.

However, pregnancy rates are much lower in older patients.

"I can tell you that [40% pregnancy rate] does not happen in my 38-year-olds. I do not use this medication in women over 40. I feel that we are just wasting time."

However, in well-selected young patients, the strategy is worth a try, since it is inexpensive, easy, and not associated with an unacceptable rate of multiple births.

"For a generalist, this is a safe drug to use for 3-4 cycles, particularly in younger patients. Then move that patient on," Dr. Miller said. ■

Patient Trust Is the Key to Getting Infertility Facts Across

BY BETSY BATES
Los Angeles Bureau

SAN FRANCISCO — Ob.gyns. and family physicians play a critical role in educating patients and their partners about infertility, doing a basic workup, and knowing when to refer them without delay to a specialist, according to Dr. Charles Miller.

Receiving factual information from a trusted source will go far to combat deeply entrenched myths and misconceptions about infertility, said the Naperville, Ill., infertility specialist and surgeon during Perspectives in Women's Health sponsored by OB.GYN. NEWS.

"We are not reaching them," he said. "Despite Redbook and Oprah and Marie Claire ... Time magazine, Newsweek, and U.S. News and World Report, we're just not getting there."

Dr. Miller said he was "shocked" to learn from a recent national survey sponsored by the National Infertility Association RESOLVE that the majority of women could not define infertility and believed the No. 1 cause of the problem was stress.

Among the facts women need to know:

► Infertility is defined as failure of a woman 35 or younger to become pregnant in 1 year, or in 6 months if the woman is over 35.

► Fecundity rates decline quite precipitously after the first six cycles of attempting to achieve pregnancy.

► There are 7.7 million couples experiencing infertility in the United States today.

► One in three U.S. couples aged 35-39 years will not be able to achieve pregnancy without treatment.

► The risk of Down syndrome and other chromosomal abnormalities increases sharply as women age: estimated to be 1 in 11 live births and 1 in 8 live births, respectively, in a woman who delivers at age 49.

► The live-birth rate for in vitro fertilization in women over the

age of 40 is approximately 10%-15% at most centers.

Dr. Miller pointed out that the age-related decline in fertility has been documented since the 17th century. "This is nothing new. This is not because of STDs, not because of more fibroids, not because of diet. This is because of egg production."

Most of the causes of infertility are physical, not psychological, he said.

Among female factors, ovulatory factors are responsible for infertility in about a third of patients, uterine and tubal factors combine to contribute to about 40% of cases, and endocrine factors are responsible for about 17%.

Varicocele is most commonly behind male infertility, but idiopathic factors, obstruction (14%), and other causes, including infections, medications, and immunologic problems, are also factors.

Debate rages about whether immunologic concerns are a major contributor to infertility. Dr. Miller called the issue "probably the raciest part of our field."

He said he believes anticardiolipin antibodies probably do hamper fertility, but the role of other antiphospholipid antibodies is less clear.

"There are physicians who will work this up to the hilt, and there are groups of physicians who will ignore it," he said. ■