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# Aging and Infertility in Women

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## STATEMENT OF NEED

A relatively large group of women is experiencing age-related infertility, because of social trends that lead to deferred childbearing. Age-related female infertility results from genetic oocyte abnormalities associated with decreased ovarian reserve. Central to the infertility evaluation of women of advanced reproductive age is an assessment of ovarian reserve. It is important that those treating women with possible age-related infertility understand each clinical test to estimate ovarian reserve, including follicle-stimulating hormone and estradiol levels in the early follicular phase or a clomiphene citrate challenge test, as each test must be timed properly to the cycle. In addition, clinicians need to understand each test's results and limitations to discuss them with and counsel patients appropriately.

## TARGET AUDIENCE

Nurses whose primary interest is women's health and infertility.

## LEARNING OBJECTIVES

After completing this activity, the reader should be able to:

- Discuss the impact of age-related female infertility and the importance of the infertility evaluation
- Compare and contrast ovarian reserve testing methods
- Apply the implications of ovarian reserve test results to patient counseling

## CONTINUING NURSING EDUCATION ACCREDITATION AND CONTACT HOURS STATEMENT

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Female fertility begins to decline many years before the onset of menopause, despite continued regular ovulatory cycles. Although there is no strict definition of advanced reproductive age in women, infertility clearly becomes more common beginning at age 35 years. As discussed in the classic American Society for Reproductive Medicine Practice Committee report,<sup>1</sup> Menken and colleagues showed that the effect of female age on fertility was such that the percentage of women not using contraception who remained childless increased steadily according to their age at marriage: 6% at ages 20 to 24 years, 9% at ages 25 to 29 years, 15% at ages 30 to 34 years, 30% at ages 35 to 39 years, and 64% at ages 40 to 44 years.<sup>2</sup> Similarly, a sharp decline in pregnancy rate with advancing female age has been noted in studies on donor insemination (which controlled for fertility of the male partner and coital frequency) and in vitro fertilization (IVF). The risk for spontaneous abortion also increases with female age, as does the risk for giving birth to a child with aneuploidy.<sup>3</sup>

A recent review of studies on the effects of male age on semen quality and fertility showed that increasing age is associated with a decline in semen volume, sperm motility, and sperm morphology, but not sperm concentration. Male fertility declines with age—particularly in men aged 50 and older—but the results of many of these studies were confounded by female partner age. There is no absolute age at which men cannot father a child. A couple's fertility, therefore, is impacted more by the age of the female partner than by the age of the male partner.<sup>4</sup>

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## The Impact of Age

The average age of childbearing has increased over the past 3 decades, as more women have pursued higher education and careers and have postponed marriage. At the same time, the baby boom generation contains a large number of women currently in their late reproductive years, thus increasing the number of women in this age-group seeking assistance for infertility. Not all women of advanced reproductive age who wish to conceive experience infertility. But, older women who present to physicians for infertility may have fertility problems in addition to a decrease in oocyte quantity and quality.

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**Age does not appear to have a significant impact on the ability of the endometrium to respond to exogenous hormone therapy. Therefore, there is no age-related decline in IVF cycle delivery rates with oocyte donation.**

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Menopause reflects near-complete depletion of the oocyte pool. However, subtle changes in early follicular phase serum concentrations—including increases of follicle-stimulating hormone (FSH) and estradiol, and decreases in inhibin B and anti-Müllerian hormone (AMH)—precede changes in menstrual regularity and ovarian hormone production. Risk factors for early decrease in

ovarian reserve include smoking, family history of premature ovarian failure/early menopause, significant ovarian pathology (ie, endometriosis), and previous ovarian surgery.<sup>5</sup>

Age-related decline in female fertility and increased risk for spontaneous abortion are largely attributable to genetic abnormalities in the oocyte. The meiotic spindle in the oocytes of older women frequently exhibit abnormalities in chromosome alignment and microtubular matrix composition. Higher rates of single chromatid abnormalities in oocytes, as well as aneuploidy in preimplantation embryos and ongoing pregnancies, are observed often in older women. The higher incidence of oocyte aneuploidy is the major cause of increased spontaneous abortion and decreased live-birth rates in women of advanced reproductive age.<sup>6</sup> The prevalence of uterine pathology, such as fibroids and endometrial polyps, also increases with age. Little evidence suggests, however, that uterine factors have a significant impact on age-related infertility. In addition, age does not appear to have a significant impact on the ability of the endometrium to respond to exogenous hormone therapy. Therefore, there is no age-related decline in IVF cycle delivery rates with oocyte donation.

## Infertility Evaluation

Tests to evaluate infertility provide information about current fertility, but do not predict when the onset of age-related infertility will occur. Infertility often is defined as the inability to conceive after 1 year of unprotected intercourse; however, earlier evaluation of infertility is warranted in women aged

activity. Disclosures are as follows:

- Dawn Lagrosa has nothing to disclose.
- Aaron S. Lifchez, MD, has nothing to disclose.
- Jessica Smith has nothing to disclose.
- The staff members of Science Care have nothing to disclose.

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older than 35 years. The consequences of undiagnosed infertility factors can be more detrimental to women who have limited time to achieve a successful pregnancy. In addition to infertility testing, the preconception medical evaluation should include screening for significant medical disorders, which are more frequent in older women. In women aged 40 years and older, it is advisable to perform mammography before attempting pregnancy, because infertility medications can increase the risk for breast cancer.

Central to the infertility evaluation of women of advanced reproductive age is an assessment of ovarian reserve. The term ovarian reserve describes a woman's reproductive potential with respect to oocyte quantity, and more importantly, oocyte quality.

#### Ovarian Reserve Testing

Ovarian reserve assessment methods fall into 2 categories: passive testing and dynamic testing. The goal of both approaches is to provide information regarding oocyte quality and quantity. Passive methods include cycle day-3 FSH and estradiol, inhibin B, AMH, as well as baseline ultrasound for antral follicle count and ovarian volume. The most commonly used dynamic test is the clomiphene citrate challenge test (CCCT).

**FSH and estradiol.** The earliest test of ovarian response was the cycle day-3 FSH test, later followed by the cycle day-3 estradiol test. If the FSH or estradiol level is high on cycle day 3, patients are more likely to respond poorly to stimulation with gonadotropins and have greatly reduced pregnancy rates with both IVF and ovulation induction with intrauterine insemination (IUI).<sup>7</sup> This results from the aging follicle's failure to produce adequate amounts of inhibin, a hormone that feeds back to the pituitary to suppress FSH production. If the FSH level is elevated earlier in the cycle, the estradiol level also will elevate. An earlier and more marked rise in FSH level will result in earlier follicular recruitment and a shortened follicular phase of the cycle. As a rule, the FSH level should be <8 mIU/mL and the estradiol level should be <70 pg/mL.<sup>8</sup>

**Inhibin B.** Levels of inhibin B in cycle day-3 serum offer a newer measure for ovarian reserve. Inhibin B is secreted by the granulosa cells of the ovarian follicle in response to gonadotropins. Inhibins have been defined based on their activity of suppressing pituitary gonadotropin secretion. Thus, the serum concentrations of inhibin B and FSH are related inversely and, at low serum levels of inhibin B, FSH concen-

tration increases. During a normal menstrual cycle, inhibin B serum concentration increases gradually in the follicular phase to a broad peak at 7 days before the luteinizing hormone surge, and may constitute the limiting factor for the duration of the intercycle FSH rise. It has been established that FSH secretion is controlled by inhibin B and thus, inhibin B measurement is a more direct way of assessing follicular functions rather than FSH alone. Whereas FSH is a response to ovarian function, inhibin B is expressed as an ovarian function of the granulosa cells of the ovary.<sup>9</sup> For normal inhibin B, the level should be  $\geq 45$  pg/mL.<sup>10</sup>

**AMH.** AMH, a protein hormone structurally related to inhibin, is expressed by the granulosa cells of the follicle during reproductive age and controls the formation of primary follicles by inhibiting excessive follicular recruitment by FSH. It, therefore, has a role in folliculogenesis. Substantial evidence exists that AMH levels correlate better with ovarian reserve than either FSH or inhibin B levels and, as a consequence, AMH rapidly is surpassing FSH as a more reliable and valid tool to measure ovarian reserve.<sup>11</sup> In addition, AMH, unlike FSH, does not require a feedback mechanism. Therefore, it can be measured at any time in the cycle and acts as a reliable indicator of ovarian reserve even while a woman is taking combined oral contraceptive pills. Although not an absolute, a "comfortable" AMH level is in the range of 1 ng/mL to 3.5 ng/mL. Levels <1 ng/mL are worrisome, and levels >5 ng/mL suggest the possibility of polycystic ovaries.<sup>12</sup>

**Antral follicle count and ovarian volume.** Another reliable method for ovarian reserve testing uses transvaginal ultrasound. At the beginning of a menstrual cycle, ultrasound imaging allows for visualization and measurement of small follicles available to respond to stimulation in the ovary. A normal follicle will be <10 mm in diameter. Studies have demonstrated that as a woman ages, the visible number of these follicles at the beginning of the menstrual cycle decreases significantly.<sup>13</sup> This reduction likely represents a decrease in the number of viable eggs that remain in the ovary. This theory is based on the observation that women with a diminished antral follicle count respond poorly to fertility medications and have a greater likelihood of having IVF cycles cancelled because of a poor response to stimulation. In addition, when these women complete IVF cycles, their pregnancy rates are lower. Studies differ on the exact number of follicles that would be considered

decreased, but most experts agree that a total number <8 should be considered a decreased antral follicle count. As the oocytes are being "lost," the ovaries become smaller and, as a consequence, decreased ovarian volume also correlates with decreased ovarian reserve. Using transvaginal ultrasound, the volume of each ovary can be calculated by measuring the length, width, and depth. Normal dimensions generally are considered to be 1.5 cm x 2 cm x 3.5 cm.<sup>13</sup>

**CCCT.** With this test, clomiphene citrate is given at a dose of 100 mg on days 5 through 9 of the cycle and FSH levels are determined on days 3 and 10. An estradiol level can be done on cycle day 3 as well, to add supportive diagnosis. Various cutoff values have been reported, because of the various laboratory techniques used (and the evolution of international standards for FSH since the time the test was introduced).<sup>8</sup> In my opinion, an FSH level >10 mIU/mL for either day 3 or day 10 indicates

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**It is important to note that a single elevated cycle day-3 FSH value connotes a poor prognosis.**

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abnormal test results. The rationale for the test is simple. The cycle day-3 value is unstimulated and represents the same basal value used in the cycle day-3 FSH screening, as described. Clomiphene stimulates an increased release of FSH early in the follicular phase, which improves follicular function and, when normal, the follicle produces enough inhibin and estradiol to feed back to the pituitary negatively and suppress FSH production by cycle day 10. Clomiphene adds a provocative element, which uncovers patients who may otherwise not be detected with basal FSH screening. As a practical matter, however, our clinic currently performs CCCT tests on very few patients.

#### Patient Counseling

Regardless of testing methods used, there are several caveats about test results. First, if the test result shows as normal, for example, in a 35-year-old woman, it does not mean that the ovaries are normal for her age. The only conclusion that can be drawn is that the ovaries are functioning similarly to a woman aged <43 years. That patient could enter diminished reserve in 1 or 10 years. Second, studies that have evaluated the tests carefully have not found a stratification of normals and abnormal; test results show as either



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positive or negative. In women aged older than 40 years, there are few reported cases of an abnormal test associated with a successful pregnancy. These patients then can be counseled definitively that alternative treatments to "own-egg IVF," such as donor-egg IVF or adoption, must be considered.

Decreased ovarian reserve at any age portends a poor prognosis to treatment including the use of IVF, the most efficacious infertility treatment available today. Alternative stimulation protocols have been proposed, but significant improvements in the pregnancy rate are lacking in patients with diminished ovarian reserve. It has been proposed that even before a clinically detectable abnormal test result, ovarian reserve is declining. Therefore, a significant portion of the population with unexplained infertility who would have a positive test and then an undisclosed number who are nearing the period of diminished ovarian reserve, have abnormal ovarian function.

Women with abnormal results for basal FSH testing, estradiol testing, or CCCT have lower live-birth rates with ovulation induction and IUI. Women with diminished ovarian reserve also experience decreased responses to ovulation induction, require higher doses of gonadotropin, have higher IVF cycle cancellation rates, and experience lower pregnancy rates through IVF,<sup>14</sup> as well as a higher incidence of spontaneous abortion. It is important to note that a single elevated cycle day-3 FSH value connotes a poor prognosis, even when values in subsequent cycles are normal.

As a result, preconception counseling for women aged 35 years and older should include a discussion of the increased risks for aneuploidy, spontaneous abortion, and obstetric complications, such as delivery by cesarean section, hypertension, and gestational diabetes associated with increasing maternal age. Counseling after ovarian reserve testing should include a discussion of the implications of the results. Although they may predict a lower pregnancy rate, abnormal ovarian re-

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## Aging and Infertility... *Continued from page 21*

serve test results do not preclude the possibility of pregnancy, and should not be presented to patients as absolute. Likewise, ovarian reserve testing alone may yield falsely reassuring results, because advanced maternal age and ovarian reserve test results are independent predictors of infertility. Both should be used when counseling couples regarding their chances for conception and a successful pregnancy.

### Treatment Options

Treatment options for age-related infertility include controlled ovarian hyperstimulation (COHS) with IUI, IVF, and oocyte donation. Aside from oocyte donation, these treatments are intended to accelerate the time to conception rather than to directly affect oocyte or embryo quality. Expectant management—which should be reserved for couples who do not desire medical intervention—is also considered a treatment option, but is less likely to result in pregnancy in women of advanced reproductive age.

COHS/IUI has limited efficacy for women aged older than 40 years with otherwise unexplained infertility, yielding a per-cycle delivery rate of 5% or less, compared with a live-birth rate per cycle of 17% to 22% for women aged younger than 35, and 8% to 10% for women aged 35 to 40 years.

The presence of male-factor infertility, tubal disease, endometriosis, or pelvic adhesions would argue for proceeding directly to IVF in women of advanced reproductive age. Pregnancy

rates from IVF are generally higher than from COHS/IUI, but these also decline significantly with age. According to the 2006 national summary of IVF success rates published by the Society for Assisted Reproductive Technologies, live-birth rates per cycle were 38.8% in women aged younger than 35 years, 30.6% in women aged 35 to 37 years, 19.7% in women aged 38 to 40 years, 10.9% in women aged 41 to 42 years, and approximately 4.3% in women aged 43 years and older.<sup>15</sup>

A recent multicenter review of 431

### TAKEAWAY QUICK POINTS

- ▶ A relatively large group of women is experiencing age-related infertility, because of social trends that lead to deferred child-bearing.
- ▶ Age-related infertility is a result of genetic oocyte abnormalities associated with decreased ovarian reserve.
- ▶ Clinical tests to estimate ovarian reserve include follicle-stimulating hormone and estradiol levels in the early follicular phase (cycle days 2-4) or a clomiphene citrate challenge test.
- ▶ Evaluation and treatment of infertility in women aged 35 years and older should not be delayed.
- ▶ With evidence of decreased ovarian reserve at any age, infertility treatment should be aggressive.

initiated IVF cycles in women aged 41 years and older showed no clinical pregnancies in women aged 45 years or older and no deliveries in women aged older than 43 years. This age-related decline in IVF success is related to decreased ovarian responsiveness to gonadotropins and, more importantly, to a marked decline in embryo implantation rates. Embryonic aneuploidy is likely the major reason for implantation failure in older women.<sup>16</sup>

Many alternative approaches have been attempted in women with decreased ovarian reserve. Unfortunately, there are no randomized trials to compare the relative efficacy of these approaches. Exclusion of aneuploid embryos with preimplantation genetic diagnosis lowers the spontaneous abortion rate in IVF cycles, but it does not lower the pregnancy rate. However, the technique is expensive and generally not covered by insurance, even for women who have an infertility benefit.

Oocyte donation is clearly the most effective treatment for infertility in women aged older than 40 years, and for younger women with compromised ovarian reserve. Although the resulting child will not be biologically related to the birth mother, oocyte donation yields the highest live-birth rate of any assisted reproductive technology treatment. It is the treatment of choice for age-related infertility not successfully addressed by other methods. Pregnancy rates with oocyte donation are dependent on the age of the donor rather than the recipient. ■

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## WOMEN'S HEALTH

# Lifestyle Intervention Does Not Appreciably Improve Obstetric and Neonatal Outcomes in Obese Women

By Alice Goodman

San Diego, CA—Obese pregnant women realized a modest improvement in weight control when they participated in a lifestyle intervention in a randomized, controlled trial presented at the 2011 American Diabetes Association Scientific Sessions. The difference in gestational weight gain was significant ( $P = .014$ ) in favor of the lifestyle intervention, but the small reduction in weight gain did not translate to significant differences in obstetric and neonatal outcomes.

“Lifestyle intervention resulted in a higher adherence to the Institute of Medicine weight gain recommendations. However, despite the intervention, a significant number of women

still exceeded the upper threshold for weight gain during pregnancy,” said presenter Christina A. Vinter, MD, of the Odense University Hospital, Denmark.

Approximately one third of pregnant women in Denmark are overweight, and more than 12% are obese, having a body mass index (BMI) of  $\geq 30$  kg/m<sup>2</sup>. Obesity during pregnancy increased the risk for gestational diabetes, hypertensive complications, cesarean sections, and infants born larger for gestational age.

The researchers randomized 360 obese women with a BMI of 30 to 45 kg/m<sup>2</sup> to either lifestyle intervention or the control group during early pregnancy. Women randomized to the lifestyle

intervention group received dietary guidance, free membership in fitness centers, physical training, and personal coaching in group situations. Dietary guidance included individual counseling and calorie restriction to a goal of 5 kg weight gain during pregnancy; physical activity included 30 to 60 minutes of daily physical exercise, weekly aerobic classes, and group coaching.

In total, 150 women in the intervention group and 154 in the control group completed the study. At week 35 of gestation, overall gestational weight gain was 7 kg in the intervention group versus 8.6 kg in the control group; gestational weight gain of  $\leq 5$  kg was seen in 28.5% and 20% of the women, respec-

tively; gestational weight gain of  $\leq 9$  kg was observed in 64.6% and 53.4%, respectively.

At week 35 of gestation, systolic and diastolic blood pressures were similar between the 2 groups, as was physical fitness level. Obstetric and neonatal outcomes were not significantly different between groups.

“These results suggest that, since the intervention had no clear effect on clinical outcomes, lifestyle intervention should probably be considered [for obese women] prior to getting pregnant to optimize obstetric and neonatal outcomes,” Dr Vinter said, “but further studies of intervention are needed to draw firm conclusions.” ■