Ovarian Aging May Be Missed as Infertility Cause

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ASHEVILLE, N.C. — Ovarian aging is often overlooked as a cause of infertility and should be considered even in younger women, Dr. Tamer M. Yalcinkaya said at the Southern Obstetric and Gynecologic Seminar.

Dr. Yalcinkaya, medical director of the in vitro fertilization program at Wake Forest University, Winston-Salem, N.C., said that ovarian aging is an evolving concept. It encompasses age-related infertility, diminished ovarian reserve, and early ovarian aging.

Ovarian aging often is hidden among the "unexplained" causes of infertility, but it is as common as many of the factors usually examined and is more severe and less treatable, said Dr. Yalcinkaya.

Ovarian aging is usually a result of progressive follicular depletion and/or abnormalities in the oocyte/follicle. Oocytes are continually declining from birth to menopause, but the decrease accelerates starting at age 38, he said, citing a 2005 study (N. Engl. J. Med. 2005;353:64-73). At the same time, there is an increase in basal follicle-stimulating hormone (FSH) levels, a decrease in fecundity, and an increase in aneuploidy. While endocrine and menstrual functions remain relatively unchanged for the next 6-8 years, menstrual irregularities generally begin at 45. By menopause, there are 1,000 or fewer follicles. The mean age of menopause is 51, though it ranges from 40 to 60. The age of onset is primarily determined by genetic factors but is slightly influenced by lifestyle, environmental, and parity factors.

Ten percent of the population will have early menopause—that is, by age 45—and another 10% will show early ovarian aging, when they are aged 27-32, said Dr. Yalcinkaya. Women in the normal range of reproductive age can experience ovarian aging, he said. However, women with diminished ovarian reserve still have the potential to conceive, and it is important to identify these women early so that various assisted reproductive techniques can be attempted, said Dr. Yalcinkaya.

Diagnostics include baseline hormone measures, including early follicular phase FSH, estradiol, inhibin B, and antimüllerian hormone. Ultrasound can be used to count the number of antral follicles if the technician is experienced; it can also measure ovarian volume. A threshold of 3 cm^3 is used to predict poor outcome with in vitro fertilization, he said. FSH levels were shown to be an indirect predictor of success with in vitro fertility techniques in a study published in Fertility and Sterility (2003;79:1091-100), Dr. Yalcinkaya said. Normal is less then 10 IU/L. Measures of 10-15 indicate a moderately diminished reserve; 15-20, severely diminished; and greater than 20, the pregnancy chances are almost zero, he said.

Hormone tests should be challenged with clomiphene citrate, exogenous FSH reserve, and gonadotropin-releasing hormone agonist stimulation.

The clomiphene citrate challenge may be better at detecting diminished ovarian reserve than the FSH test but can only be used in patients over age 35, he said. Often, patients who have an abnormal clomiphene citrate test are told they have "ovulatory disorder" or "unexplained infertility," but clinicians should investigate further as to whether the cause is ovarian aging, Dr. Yalcinkaya said.

The inhibin B test is new and evolving, with divergent data on its utility, he said.

Most of these tests have a low positive predictive value; good results mean the clinician can't guarantee that the patient will become pregnant. But they also have a high negative predictive value; abnormal results generally mean a pregnancy is highly unlikely, Dr. Yalcinkaya said.

Ovarian aging can't be stopped, but physicians can counsel women to maintain healthy lifestyles that promote fertility, including quitting smoking. Physicians can also consider liberal testing of ovarian reserve in all infertile women who are over age 35 or who have a single ovary; in women with a history of ovarian surgery; and in women who smoke or have unexplained infertility, recurrent unexplained early pregnancy losses, irregular periods, or a family history of early menopause, he said. Patients with mild to moderate ovarian aging should be referred to a reproductive endocrinologist for aggressive treatment with exogenous gonadotropin and intrauterine insemination or in vitro fertilization, he said.

Dr. Yalcinkaya had no conflicts of interest to disclose. ■

ParaGard® T 380A
intrauterine copper contraceptive

Brief Summary

(See package brochure for full prescribing information)

Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

ParaGard® T 380A Intrauterine Copper Contraceptive should be placed and removed only by healthcare professionals who are experienced with these procedures.

INDICATIONS AND USAGE
ParaGard® is indicated for intrauterine contraception for up to 10 years. The pregnancy rate in clinical studies has been less than 1 pregnancy per 100 women each year.

CONTRAINDICATIONS
ParaGard® should not be placed when one or more of the following conditions exist:
1. Pregnancy or suspicion of pregnancy
2. Abnormalities of the uterus resulting in distortion of the uterine cavity
3. Acute pelvic inflammatory disease, or current behavior suggesting a high risk for pelvic inflammatory disease
4. Postpartum endometritis or postabortal endometritis in the past 3 months
5. Known or suspected uterine or cervical malignancy
6. Genital bleeding of unknown etiology
7. Mucopurulent cervicitis
8. Wilson's disease
9. Allergy to any component of ParaGard®
10. A previously placed IUD that has not been removed

WARNINGS
1. **Intrauterine Pregnancy**
If intrauterine pregnancy occurs with ParaGard® in place and the string is visible, ParaGard® should be removed because of the risk of spontaneous abortion, premature delivery, sepsis, septic shock, and, rarely, death. Removal may be followed by pregnancy loss.

If the string is not visible, and the woman decides to continue her pregnancy, check if the ParaGard® is in her uterus (for example, by ultrasound). If ParaGard® is in her uterus, warn her that there is an increased risk of spontaneous abortion and sepsis, septic shock, and rarely, death. In addition, the risk of premature labor and delivery is increased.

Human data about risk of birth defects from copper exposure are limited. However, studies have not detected a pattern of abnormalities, and published reports do not suggest a risk that is higher than the baseline risk for birth defects.

2. **Ectopic Pregnancy**
Women who become pregnant while using ParaGard® should be evaluated for ectopic pregnancy. A pregnancy that occurs with ParaGard® in place is more likely to be ectopic than a pregnancy in the general population. However, because ParaGard® prevents most pregnancies, women who use ParaGard® have a lower risk of an ectopic pregnancy than sexually active women who do not use any contraception.

3. **Pelvic Infection**
Although pelvic inflammatory disease (PID) in women using IUDs is uncommon, IUDs may be associated with an increased relative risk of PID compared to other forms of contraception and to no contraception. The highest incidence of PID occurs within 20 days following insertion. Therefore, the visit following the first post-insertion menstrual period is an opportunity to assess the patient for infection, as well as to check that the IUD is in place. Since pelvic infection is most frequently associated with sexually transmitted organisms, IUDs are not recommended for women at high risk for sexual infection. Prophylactic antibiotics at the time of insertion do not appear to lower the incidence of PID.

PID can have serious consequences, such as tubal damage (leading to ectopic pregnancy or infertility), hysterectomy, sepsis, and, rarely, death. It is therefore important to promptly assess and treat any woman who develops signs or symptoms of PID.

Guidelines for treatment of PID are available from the Centers for Disease Control and Prevention (CDC), Atlanta, Georgia at www.cdc.gov or 1-800-311-3435. Antibiotics are the mainstay of therapy. Most healthcare professionals also remove the IUD.

The significance of actinomyces-like organisms on Papanicolaou smear in an asymptomatic IUD-user is unknown, and so this finding alone does not always require IUD removal and treatment. However, because pelvic actinomycosis is a serious infection, a woman who has *symptoms* of pelvic infection possibly due to actinomyces should be treated and have her IUD removed.

4. **Immunocompromise**
Women with AIDS should not have IUDs inserted unless they are clinically stable on antiretroviral therapy. Limited data suggest that asymptomatic women infected with human immunodeficiency virus may use intrauterine devices. Little is known about the use of IUDs in women who have illnesses causing serious immunocompromise. Therefore these women should be carefully monitored for infection if they choose to use an IUD. The risk of pregnancy should be weighed against the theoretical risk of infection.

5. **Embedment**
Partial penetration or embedment of ParaGard® in the myometrium can make removal difficult. In some cases, surgical removal may be necessary.

6. **Perforation**
Partial or total perforation of the uterine wall or cervix may occur rarely during placement, although it may not be detected until later. Spontaneous migration has also been reported. If perforation does occur, remove ParaGard® promptly, since the copper can lead to intraperitoneal adhesions. Intestinal penetration, intestinal obstruction, and/or damage to adjacent organs may result if an IUD is left in the peritoneal cavity. Pre-operative imaging followed by laparoscopy or laparotomy is often required to remove an IUD from the peritoneal cavity.

7. **Expulsion**
Expulsion can occur, usually during the menses and usually in the first few months after insertion. There is an increased risk of expulsion in the nulliparous patient. If unnoticed, an unintended pregnancy could occur.

8. **Wilson's Disease**
Theoretically, ParaGard® can exacerbate Wilson's disease, a rare genetic disease affecting copper excretion.

PRECAUTIONS
Patients should be counseled that this product does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

1. **Information for patients**
Before inserting ParaGard® discuss the Patient Package Insert with the patient, and give her time to read the information. Discuss any questions she may have concerning ParaGard® as well as other methods of contraception. Instruct her to promptly report symptoms of infection, pregnancy, or missing strings.

2. **Insertion precautions, continuing care, and removal.**
(See **Package Brochure for INSTRUCTIONS FOR USE**.)

3. **Vaginal bleeding**
In the 2 largest clinical trials with ParaGard® (see ADVERSE REACTIONS, Table 2), menstrual changes were the most common medical reason for discontinuation of ParaGard®. Discontinuation rates for pain and bleeding combined are highest in the first year of use and diminish thereafter. The percentage of women who discontinued ParaGard® because of bleeding problems or pain during these studies ranged from 11.9% in the first year to 2.2 % in year 9. Women complaining of heavy vaginal bleeding should be evaluated and treated, and may need to discontinue ParaGard®. (See **ADVERSE REACTIONS**.)

4. **Vasovagal reactions, including fainting**
Some women have vasovagal reactions immediately after insertion. Hence, patients should remain supine until feeling well and should be cautious when getting up.

5. **Expulsion following placement after a birth or abortion**
ParaGard® has been placed immediately after delivery, although risk of expulsion may be higher than when ParaGard® is placed at times unrelated to delivery. However, unless done immediately postpartum, insertion should be delayed to the second postpartum month because insertion during the first postpartum month (except for immediately after delivery) has been associated with increased risk of perforation.

ParaGard® can be placed immediately after abortion, although immediate placement has a slightly higher risk of expulsion than placement at other times. Placement after second trimester abortion is associated with a higher risk of expulsion than placement after the first trimester abortion.

6. **Magnetic resonance imaging (MRI)**
Limited data suggest that MRI at the level of 1.5 Tesla is acceptable in women using ParaGard®. One study examined the effect of MRI on the CU-7® Intrauterine Copper Contraceptive and Lippes Loop™ intrauterine devices. Neither device moved under the influence of the magnetic field or heated during the spin-echo sequences usually employed for pelvic imaging. An in vitro study did not detect movement or temperature change when ParaGard® was subjected to MRI.

7. **Medical diathermy**
Theoretically, medical (non-surgical) diathermy (short-wave and microwave heat therapy) in a patient with a metal-containing IUD may cause heat injury to the surrounding tissue. However, a small study of eight women did not detect a significant elevation of intrauterine temperature when diathermy was performed in the presence of a copper IUD.

8. **Pregnancy**
ParaGard® is contraindicated during pregnancy. (See CONTRAINDICATIONS and WARNINGS.)

9. **Nursing mothers**
Nursing mothers may use ParaGard®. No difference has been detected in concentration of copper in human milk before and after insertion of copper IUDs. The literature is conflicting, but limited data suggest that there may be an increased risk of perforation and expulsion if a woman is lactating.

10. **Pediatric use**
ParaGard® is not indicated before menarche. Safety and efficacy have been established in women over 16 years old.

ADVERSE REACTIONS
The most serious adverse events associated with intrauterine contraception are discussed in **WARNINGS** and **PRECAUTIONS**. These include:

Intrauterine pregnancy
Septic abortion
Ectopic pregnancy
Pelvic infection
Perforation
Embedment

Table 2 shows discontinuation rates from two clinical studies by adverse event and year.

Table 2. Summary of Rates (No. per 100 Subjects) by Year for Adverse Events Causing Discontinuation

Adverse Event	Year									
	1	2	3	4	5	6	7	8	9	10
Pregnancy	0.7	0.3	0.6	0.2	0.3	0.2	0.0	0.4	0.0	0.0
Expulsion	5.7	2.5	1.6	1.2	0.3	0.0	0.6	1.7	0.2	0.4
Bleeding/Pain	11.9	9.8	7.0	3.5	3.7	2.7	3.0	2.5	2.2	3.7
Other Medical Event	2.5	2.1	1.6	1.7	0.1	0.3	1.0	0.4	0.7	0.3
No. of Women at Start of Year	4932	3149	2018	1121	872	621	563	483	423	325

*Rates were calculated by weighting the annual rates by the number of subjects starting each year for each of the Population Council (3,536 subjects) and the World Health Organization (1,396 subjects) trials.

The following adverse events have also been observed. These are listed alphabetically and not by order of frequency or severity.
Anemia
Backache
Dysmenorrhea
Dyspareunia
Expulsion, complete or partial
Leukorrhea
Menstrual flow, prolonged
Menstrual spotting
Pain and cramping
Urticarial allergic skin reaction
Vaginitis

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