Winter 2016

Cleveland Clinic

Ob/Gyn & Women's Health Perspectives

An Update for Physicians from Cleveland Clinic's Ob/Gyn & Women's Health Institute

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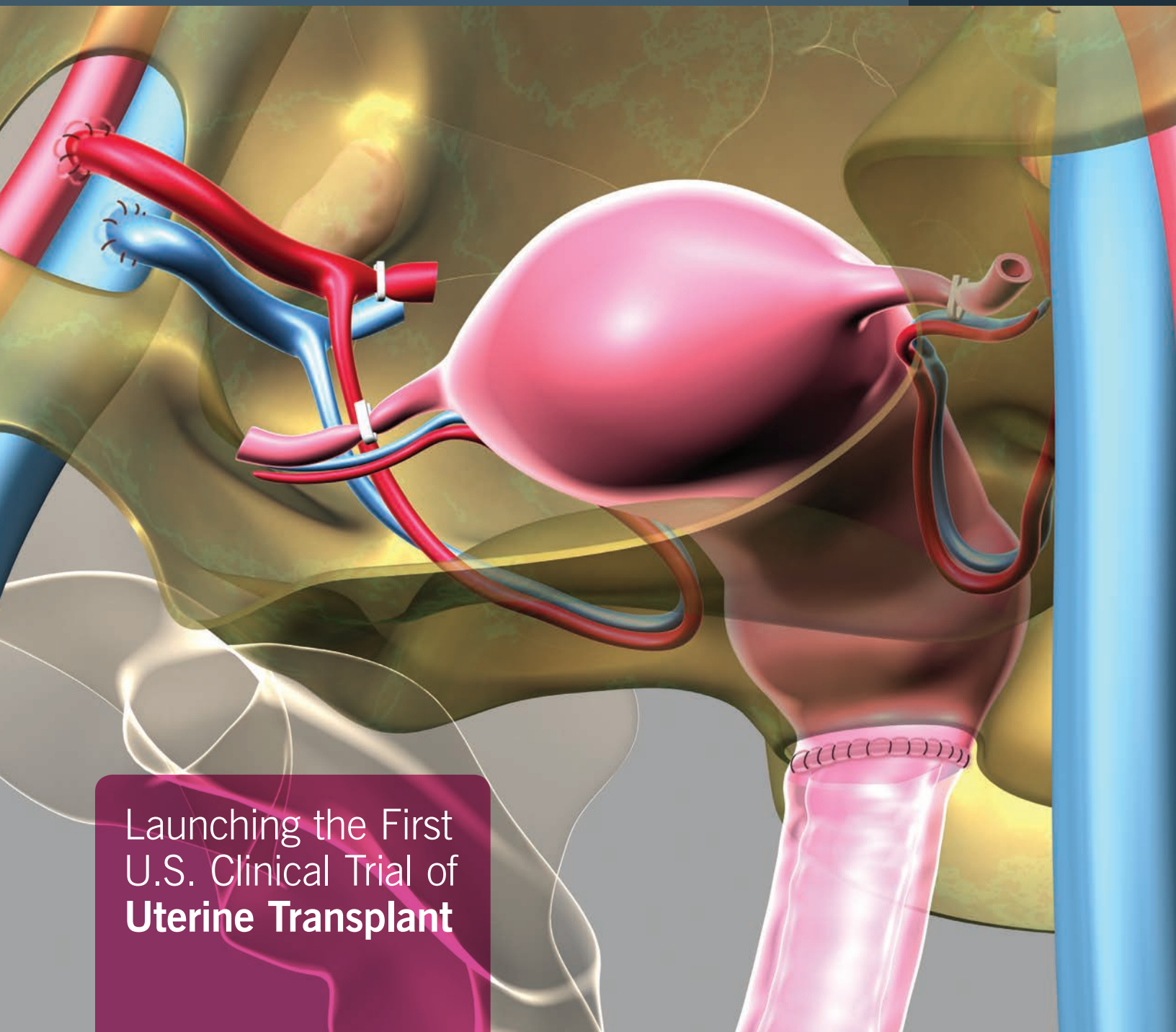

Launching the First U.S. Clinical Trial of **Uterine Transplant**

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Cleveland Clinic's Gynecology program is ranked No. 3 in the nation by *U.S. News & World Report*.

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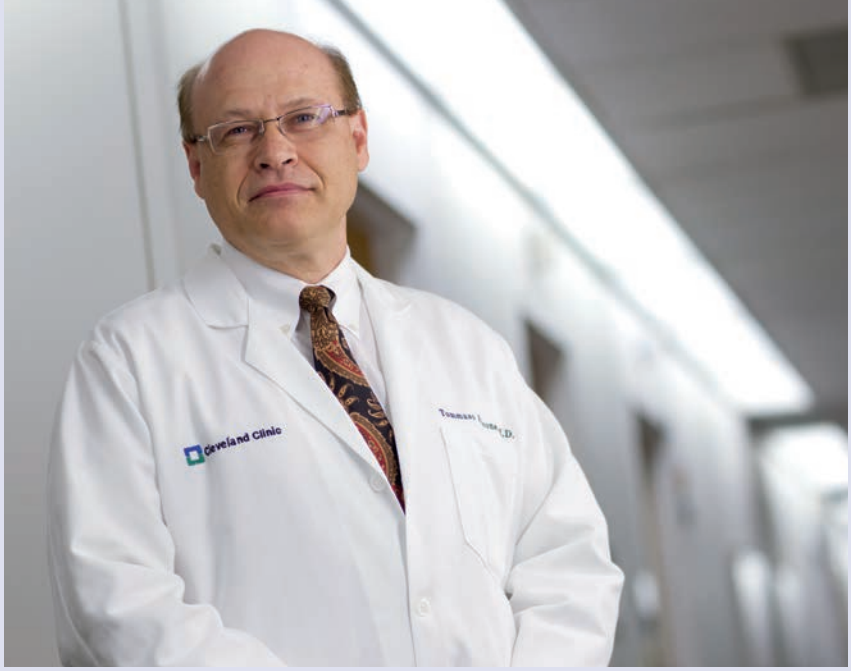


Dear Colleagues and Friends:

Welcome to the Winter 2016 issue of *Ob/Gyn & Women's Health Perspectives*. We are excited to announce that Cleveland Clinic is the first U.S. medical center to enroll patients in a clinical trial of uterine transplant.

Our cover story describes this novel study. It is a product of many years of research, in which we collaborated with the team at University of Gothenberg in Sweden; the expertise of our medical teams; and the support of our organization.

In this edition, you will also read about:

- **Cancer genomics and precision oncology:** Haider Mahdi, MD, MPH, discusses advances in DNA sequencing technology that make it possible to identify genomic alterations for targeted therapy.
- **Endometrioma surgery and ovarian reserve:** Preliminary findings from a prospective study that Linnea Goodman, MD, and I led suggest a need for conservative surgical management of endometriomas in subfertile women.
- **Vulvovaginitis Clinic:** Oluwatosin Goje, MD, explains the complex differential diagnosis involved and how streamlined management helps patients with chronic issues.

I hope you enjoy this edition of *Ob/Gyn & Women's Health Perspectives* and find information that is useful for your practice. As always, our team welcomes your comments and feedback, and values our ongoing collaboration with you.

Sincerely,

Tommaso Falcone

Tommaso Falcone, MD, FRCSC, FACOG
Professor & Chairman, Department of Obstetrics and Gynecology
Chairman, Ob/Gyn & Women's Health Institute

Vulvovaginitis: New Clinic Eases Diagnosis and Management

By Oluwatosin Goje, MD, MSCR

Vulvovaginitis is one of the major reasons women visit their healthcare providers every year. Infection or inflammation of the vulva and vagina costs the U.S. economy more than $10 billion annually.

Our Center for Vulvar and Vaginal Disorders was created to better serve, treat and educate women affected by these conditions. The Vulvovaginal Health Clinic, an integral part of the center, is designed to meet the needs of women with chronic issues.

A wide-ranging differential

The most common presenting symptoms of vulvovaginitis are a malodorous discharge, pruritus, a burning sensation and evidence of vulvar irritation (such as erythema and excoriation).

Physiologic/normal vaginal secretion must be differentiated from abnormal vaginal discharge as well as contact or allergic dermatitis, vaginal atrophy, desquamative inflammatory vaginitis and even parasitic infestation.

A differential diagnosis should also include the many noninfectious causes of vaginitis and vulvitis, including lichen sclerosus, lichen planus and vulvar intraepithelial neoplasia.

Common diagnostic challenges

Recurrent vaginitis and vulvitis can be difficult to diagnose and to manage. A postmenopausal woman with symptoms of pain and burning was treated unsuccessfully for genital herpes simplex virus infection for two years. She found relief in our clinic after a thorough history, examination and vulvar biopsy revealed lichen sclerosus and lichen planus.

Patients with vulvar lichen disease are sometimes misdiagnosed as having vulvar yeast infection because pain and itching are commonly reported for both conditions.

Common Causes

INFECTIOUS	NONINFECTIOUS
› Bacterial vaginosis	› Desquamative inflammatory vaginitis
› Vulvovaginal candidiasis	› Atrophic vaginitis
› *Trichomonas*	› Urogenital manifestation of Behcet syndrome
› Herpes simplex virus	› Lichen
	› Contact/chemical/radiation dermatitis
	› Vulvar/vaginal malignancies
	› Parasitic infestation
	› Vulvodynia

In addition, contact dermatitis may look like a yeast infection that does not respond to regular antifungal treatment.

Our clinic also provides management for difficult, recurrent and/or resistant infectious causes of vulvovaginitis.

Conditions treated

Conditions treated in our clinic include:

- Recurrent bacterial vaginosis
- Recurrent *Candida* infections
- Resistant trichomoniasis
- Chronic vaginitis
- Atrophic vaginitis
- Lichen sclerosus
- Lichen planus
- Condyloma acuminata
- Recurrent genital herpes simplex infection
- Hidradenitis suppurativa
- Allergic and contact vulvar dermatitis
- Vulvar dermatoses
- Vulvar ulcers
- Sexually transmitted infections

Signs of Vulvovaginitis

- Vulvar erythema or edema
- Vulvar excoriation, fissure, pustules or vesicles
- Malodorous, grayish homogenous discharge; clumping, cheesy/thick cream discharge; thin, copious white discharge; frothy white discharge; thick, yellow mucoid discharge
- Hypopigmentation, depigmentation
- Vulvar atrophy or vulvar lichenification
- Vaginal erythema

We see patients referred by Ob/Gyns and primary care providers and patients who self-refer. To refer a patient to the Vulvovaginal Health Clinic, please call 216.445.2720. ■

Dr. Goje directs the Center for Vulvar and Vaginal Disorders and the Vulvovaginal Health Clinic. She may be reached at 440.312.2229 or at gojeo@ccf.org.

Study Suggests Decline in Ovarian Reserve for Women Undergoing Surgery for Endometriomas

By Linnea R. Goodman, MD, and Tommaso Falcone, MD

Preliminary results of a prospective evaluation suggest that surgical resection of ovarian endometriomas may precipitate a substantial, persistent decline in ovarian reserve.

Endometriosis, affecting up to 2 percent of women of reproductive age, can be asymptomatic but often causes pain and/or infertility. Researchers hypothesize that the mere presence of endometriomas — cysts that form when the ovaries are involved — may have a detrimental effect on ovarian reserve.

Resection for fertility controversial

While surgery offers definitive treatment, removal of endometrioma(s) for fertility purposes remains controversial due to concerns that cyst removal may damage healthy ovarian tissue, further decreasing ovarian reserve.

Anti-Mullerian hormone (AMH) has proved to be a reliable surrogate marker of ovarian reserve. Despite extensive scientific exploration, however, the relationship between pelvic endometriosis and AMH levels remains uncertain.

Studies on the impact of endometrioma excision on ovarian reserve over time have also had mixed results. However, most studies of AMH levels after endometrioma removal report a decrease in ovarian reserve, particularly with bilaterality.

No studies to date have looked at ovarian reserve before and after surgery in women with ovarian endometriomas versus a similar subfertile population whose complaints are consistent with suspected pelvic endometriosis.

Comparing AMH levels over time

The goals of our prospective cohort trial were to determine whether baseline ovarian reserve was lower in women with ovarian endometriomas than in women with only pelvic endometriotic lesions, as compared to those with negative laparoscopies; and to assess the impact of laparoscopic surgical excision of endometriomas on long-term ovarian reserve.

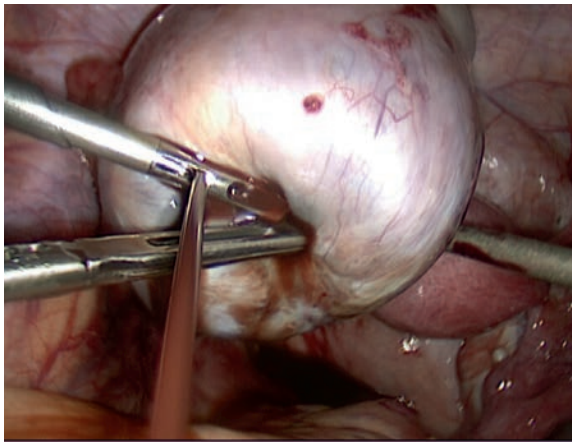
We recruited 116 patients from our reproductive endocrinology and infertility clinic. Half the women had radiological evidence of endometrioma(s). The other half had complaints (pain and/or infertility) consistent with pelvic endometriosis but no evidence of ovarian involvement on imaging.

We further segregated the control group into subjects with pathological confirmation of pelvic endometriosis on surgical exploration and subjects with no evidence of endometriosis. There were no significant differences in age, body mass index or presenting complaints between the groups.

Patients underwent AMH testing preoperatively for a baseline value, four to six weeks after surgery, and then six months postoperatively. AMH values were compared longitudinally and among groups.

Early findings suggest caution

Overall, based on preliminary results, baseline AMH values were lower in subjects with endometriomas than in subjects without endometriomas. AMH levels remained stable after surgery in subjects with only pelvic endometriosis or with negative laparoscopies. However, evidence suggested a substantial, persistent decline in ovarian reserve over the six-month follow-up for those undergoing endometrioma resection.



These preliminary results support the need for conservative surgical management in the subfertile population as ovarian endometrioma surgery may have persistent, deleterious effects on ovarian reserve. ■

To view a fully referenced version of this article, visit consultqd.org/ovarianreserve.

Dr. Falcone is Professor and Chair of Cleveland Clinic's Ob/Gyn & Women's Health Institute and may be reached at 216.444.1758 or at falcont@ccf.org.

Dr. Goodman is a fellow in the Department of Reproductive Endocrinology and Infertility and may be reached at 216.839.3150 or at goodmal3@ccf.org.

First U.S. Clinical Trial of Uterine Transplantation Begins

Pioneering concept offers hope for women with uterine factor infertility

Cleveland Clinic is the first U.S. medical center to begin screening candidates for a pioneering clinical trial of uterine transplantation in women of reproductive age with uterine factor infertility (UFI).

The IRB-approved study — the first in the United States and one of the first in the world — is spearheaded by Cleveland Clinic transplant surgeon Andreas Tzakis, MD, PhD.

"We are very excited. Uterine transplantation presents a unique option for women coping with UFI," says Dr. Tzakis. "At the same time, we are aware of the tremendous responsibility we have undertaken. This is a complex trial, and we must make sure everything we do gives our patients the best opportunity for a normal delivery."

Success in Sweden

Dr. Tzakis, who has done independent research on uterine transplantation, has been involved in an ongoing uterine transplantation trial with colleagues at the University of Gothenburg, Sweden, for years. To date, the Swedish team has performed nine uterine transplants — seven of them successful — that resulted in four live births and one on the way.

Tommaso Falcone, MD, chairman of Cleveland Clinic's Ob/Gyn & Women's Health Institute, has followed the Swedish trial closely. He is an active investigator in the field of infertility and reproductive surgery and has been interested in uterine transplantation for more than a decade.

"Adoption or maternal surrogacy are not always acceptable options for social, ethical, cultural or religious reasons," says Dr. Falcone. "Uterine transplantation is an important development that will give these women the opportunity to have a biological child."

A unique form of transplant

Uterine transplantation differs from other organ transplants in one key aspect: Because its benefit ceases after childbearing is complete, the organ is removed or allowed to be rejected after the baby or babies are born. This eliminates the need for lifelong immunosuppression and associated medical problems.

The prospect of an "ephemeral" transplant has raised ethical issues surrounding the procedure and the safety of the transplant recipients, as well as the babies born of the process. For this reason, Cleveland Clinic bioethicists were intimately involved in discussions leading to IRB approval of the clinical trial and will remain involved as the trial progresses.

Ten women, ages 21 to 39, who are infertile due to congenital uterine absence (Mayer-Rokitansky syndrome) or because their uterus was removed will be selected to receive a transplant from a deceased donor.

The Swedish study uses living donors. Cleveland Clinic is pursuing only deceased donor organs to avoid any risk to living donors.

Lifebanc, an organ procurement agency, will identify deceased donors of menstruating age with the same blood type and a healthy uterus.

Dr. Falcone and his team of gynecologists will perform a hysteroscopic examination of each donor uterus to ensure that the organ is normal and viable before it is accepted for the clinical trial and removed.

Lengthy, in-depth evaluations

For participants, the multiphase trial begins with a detailed history and physical, a fertility assessment by a reproductive gynecologist, a psychiatric review, a discussion with a bioethicist and a review of social support.

"This is a lengthy evaluation process designed to ensure each woman has the personality, social support and other circumstances that will allow a successful transplant," says John Fung, MD, PhD, Director of the Cleveland Clinic Health System Center for Transplantation.

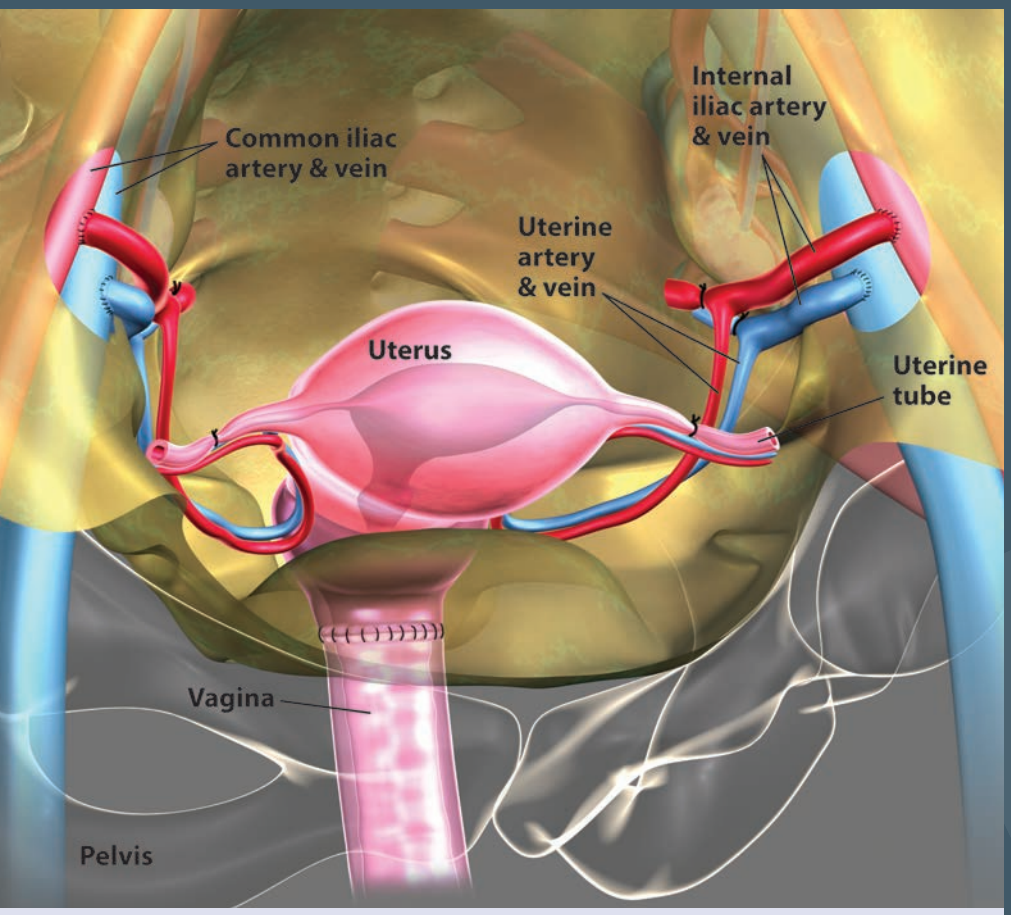
A medical examination follows. Candidates must meet all criteria in order to be accepted into the study.

Each participant will undergo ovarian stimulation, egg retrieval and in vitro fertilization with sperm in the laboratory. Once 10 viable embryos have been frozen, the patient will be put on a transplant list to await a suitable donor.

"We hope to perform the first uterine transplant next year," says Dr. Tzakis.

After assurance that the transplant has been successful and that the uterus is healthy and viable — which takes about 12 months — a fertilized embryo will be implanted. Each patient may receive up to nine embryos, which will be implanted one at a time until one to two healthy births are achieved.

"We want to make sure the uterus is mature and stable to give the embryo the best possibility for success," says Rebecca Flyckt, MD, Director of the Fertility



Preservation Program and an IVF specialist in the Ob/Gyn & Women's Health Institute. "We also think this timetable is safest for the recipient."

If an embryo results in pregnancy, the patient will be followed by Cleveland Clinic maternal-fetal medicine specialist Uma Perni, MD. Delivery will be made by caesarean section. After birth, the baby will be followed by advanced neonatologists.

It takes a team

The complexity of a uterine transplantation trial requires a team of specialists very different from the one involved in a typical organ transplant.

With an experienced transplant group and a team of adult, pediatric, neonatal and obstetric specialists accustomed to managing high-risk, complex patients, Cleveland Clinic is well-suited for this task.

Joining Dr. Tzakis, Dr. Falcone, Dr. Flyckt and Dr. Perni on the transplant team from the Ob/Gyn & Women's Health Institute are reproductive bioethicist and obstetrician Ruth Farrell, MD; gynecologic pathologist Andres Chiesa-Vottero, MD; and reproductive infectious disease specialist Oluwatosin Goje, MD. ■

Dr. Falcone may be reached at 216.444.1758 or at falcont@ccf.org; Dr. Tzakis may be reached at 954.659.5133 or at tzakisa@ccf.org.

Cancer Genomics and Precision Oncology: An Emerging Option for Personalized Gynecologic Cancer Care

By Haider Mahdi, MD, MPH

Since the Human Genome Project launched in 2002, advances in DNA sequencing technology have significantly lowered the costs and time required for cancer DNA sequencing. In addition, options such as whole-exome sequencing, RNA sequencing and targeted gene panel testing have become available.

In The Cancer Genome Atlas, a major effort by the National Cancer Institute and the National Human Genome Research Institute, next-generation sequencing was used to profile many solid tumors, including ovarian and endometrial cancers.

The wide variety of genomic alterations revealed, including gene mutations, copy number variation and structural rearrangements, can affect signaling, metabolism and gene expression within cancer cells.

The potential for biomarkers

Through these extensive efforts, we have learned the pattern of genomic alteration for several cancer types. Such alterations can impact clinical decision-making as predictive and/or prognostic biomarkers.

For example, the predictive role of the *BRAF* gene mutation in melanoma, *ALK* gene fusion in lung cancer, and the *BRCA* mutation in ovarian cancer now guide treatment selections that target these alterations.

Given these findings, the potential for treatment decisions to be personalized according to patients' genomic alterations is promising. The alterations can be unique for different cancer types and for different patients with the same cancer.

Making cancer genomic testing clinically available requires a multidisciplinary team with expertise in the entire process, from conducting genomic testing to translating genomic results to understanding the clinical evidence-based significance of genomic alterations.

Systematic review by a panel

At Cleveland Clinic, genomic tumor profiling is done at the discretion of the treating oncologist and his or her patients. Results are discussed at a weekly Genomic Tumor Board, where a panel of subspecialized oncologists and a medical geneticist reviews each patient's genomic tumor profile and the significance of any alteration.

The goal is to identify and target actionable genomic alterations with biologic therapy that is either clinically approved in this setting or under investigational clinical trials.

Genomic-based trials available

We also offer patients the opportunity to enroll in genomic-based clinical trials. For example, the National Cancer Institute recently opened a panel of phase II trials of targeted therapy based on genomic alterations for patients with any cancer. After a fresh biopsy for genomic profiling, patients with actionable genomic alterations can be enrolled into the NCI-MATCH (Molecular Analysis for Therapy Choice) trial to target that specific alteration.

Cleveland Clinic recently published its genomic tumor profiling experience with 250 patients who had selected solid tumors. Following genomic profiling and Genomic Tumor Board review, we identified actionable genomic alterations in 49 percent of them and recommended specific, targeted therapy.

Finally, advances in immunotherapy have shown evidence of the role of immunomodulators (programmed cell death-1, or PD-1, inhibitors) in ovarian and other solid cancers, especially those with genomic alterations such as MSI unstable tumors or tumors that express programmed cell death-ligand 1 (PD-L1).

A phase II national clinical trial recently finished accruing patients with recurrent ovarian cancer. We are now working to open a phase II clinical trial to correlate the efficacy of immunomodulators in recurrent endometrial cancer patients with MSI status and PD-L1 expression in tumor tissue. ■

Dr. Mahdi, a gynecologic oncologist in the Department of Obstetrics and Gynecology, may be reached at 216.445.7069 or at mahdih@ccf.org.

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In 2015, Cleveland Clinic was ranked one of America's top hospitals in *U.S. News & World Report*'s "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 21st consecutive year).

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