



Ob/Gyn & Women's Health Perspectives

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

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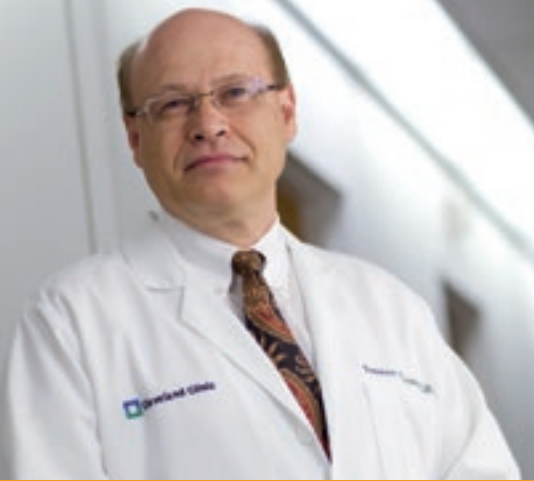
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A close-up photograph of a hand wearing a blue nitrile glove holding a syringe. The syringe is connected to a drip chamber and clear plastic tubing. The background is a blurred clinical setting with blue drapes.

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Dear Colleagues:

I appreciate your interest in Cleveland Clinic's Ob/Gyn & Women's Health Institute and your taking a few moments from your busy practice to glance through *Ob/Gyn & Women's Health Perspectives*.

In this issue, our experts discuss fibroid research, HIPEC therapy for ovarian cancer, research into preserving fertility, fetal genetic testing and the ongoing presence of the Zika virus and its concerns for pregnant women.

Since arriving at Cleveland Clinic in 1995, I have witnessed this institute's unwavering devotion to excellence and innovation in all aspects of our work — clinical care, research and education. We believe our consistently high rankings by *U.S. News & World Report* (No. 5 in the nation in 2017-2018) reflect this, and we appreciate the recognition. But even more important, this dedication to excellence and innovation has earned your trust. We thank you for the privilege of providing advanced subspecialty care for your patients.

As always, I welcome your feedback, questions and ideas for collaboration.

Tommaso Falcone

Tommaso Falcone, MD, FRCS, FACOG
Professor & Chairman, Department of
Obstetrics and Gynecology
Chairman, Ob/Gyn & Women's Health
Institute
216.444.1758 | falcont@ccf.org

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Managing Editor: Sandra Erlanger

Art Director: Amy Buskey-Wood

Photographers: Tom Merce, Russell Lee

Medical Illustrator: Ross Papalardo

Marketing: Samantha Brainard, Mindy Cannon, Suzanne Anthony, Kristin Swenson

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About Cleveland Clinic

Cleveland Clinic is an integrated health-care delivery system with local, national and international reach. At Cleveland Clinic, more than 3,500 physicians and researchers represent 120 medical specialties and subspecialties. We are a main campus, more than 150 northern Ohio outpatient locations (including 18 full-service family health centers and three health and wellness centers), Cleveland Clinic Florida, Cleveland Clinic Lou Ruvo Center for Brain Health in Las Vegas, Cleveland Clinic Canada, Sheikh Khalifa Medical City and Cleveland Clinic Abu Dhabi.

In 2017, Cleveland Clinic ranked No. 2 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 23rd consecutive year) and urologic care.

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Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Newly Diagnosed Advanced Ovarian Cancer

By Robert DeBernardo, MD

Overall survival extended by approximately 12 months

Although rare, ovarian cancer remains one of the leading causes of cancer-related death in the United States. The American Cancer Society anticipates that in 2018 more than 22,000 women will be diagnosed with and 14,000 will die from ovarian cancer. Despite recent advances in medical and surgical techniques used to treat ovarian cancer, mortality remains high because the majority of women are diagnosed at an advanced stage.

Because of ongoing treatment challenges, we are particularly encouraged by a recent trial that demonstrates extended overall survival for patients with newly diagnosed advanced ovarian cancer with the use of hyperthermic intraperitoneal chemotherapy (HIPEC).

Current treatment

Ideal treatment for advanced ovarian cancer includes complete or optimal cytoreductive surgery and platinum/taxane-based chemotherapy. Progression-free survival (PFS) and overall survival (OS) are directly linked to the amount of residual disease after surgery, with optimal surgery defined as < 1 cm residual tumor. Outcomes improve when patients have no gross residual disease.

There has been and continues to be a debate in gynecologic oncology regarding surgical timing — whether it should

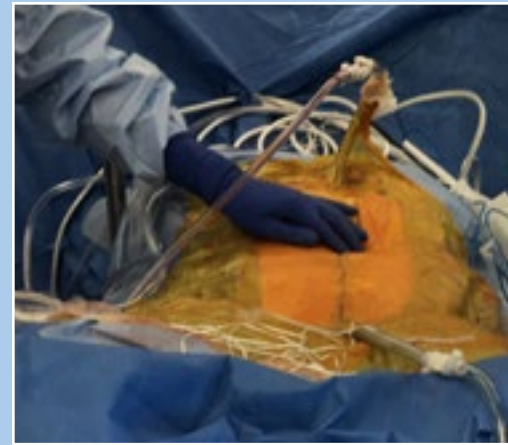
take place at presentation or after three cycles of neoadjuvant chemotherapy. A randomized trial conducted in Europe showed that cancer-related outcomes were equivalent for both time frames. However, surgical morbidity was substantially higher in women undergoing upfront surgery. The trial has been criticized for a number of reasons, leaving many experts still favoring upfront surgery. Nonetheless, we are seeing an increase in the use of neoadjuvant chemotherapy.

HIPEC at time of surgery

Using HIPEC to treat ovarian cancer has been explored at a number of centers around the world. Initially developed to treat rare chemoresistant gastrointestinal malignancies, HIPEC takes place at the time of surgery, once resection is complete. Tubing is placed in the abdomen and chemotherapy is circulated at 42 degrees Celsius. After 45 to 90 minutes, the tubing is removed and the incision closed.

What the data show for newly diagnosed cancer

Much retrospective data and, more recently, randomized data suggest there is a benefit in using HIPEC to treat women with recurrent ovarian cancer. A group from the Netherlands reported on a phase 3 randomized trial, published in the *New England Journal of Medicine*, in which women with newly diagnosed



HIPEC perfusion: Following surgical removal of all gross cancer, tubing is placed in the abdomen and the incision is closed. An assistant gently shakes the abdomen to help the heated chemotherapy circulate. After the prescribed time, the tubing is removed.

stage III ovarian cancer received HIPEC at interval surgery following neoadjuvant chemotherapy.

Their results demonstrate a significant advantage for women receiving HIPEC compared with those who didn't, with a hazard ratio of recurrence or death of 0.66 ($P = 0.003$), PFS of 14.2 versus 10.7 months and OS of 45.7 versus 33.9 months. Adverse events between the two groups were equivalent.

These data are significant because this is the first time since Gynecologic Oncology Group (GOG)-172, a randomized trial showing the benefit of intraperitoneal chemotherapy over conventional intravenous chemotherapy, that both PFS and OS were improved in a trial of women with newly diagnosed ovarian cancer.

HIPEC now on the increase

As a result of the *NEJM* study in particular, we are witnessing a number of HIPEC programs opening across the country. Our hope is that these programs offer the clinical expertise required to successfully perform cytoreductive surgery and safely administer HIPEC.

HIPEC is only effective in patients who have minimal or no residual disease after



Advances in Fetal Genetic Testing Present New Challenges to Support Patient Education and Decision-Making

By Ruth Farrell, MD, MA

surgery. The radical surgery necessary to achieve these results is generally more successful at high-volume centers with a well-established program and proven track record.

Cleveland Clinic experience

The Cleveland Clinic Ob/Gyn & Women's Health Institute team managed 144 ovarian cancer surgical cases in 2017, with outcomes above the national average. We have offered HIPEC to select women with advanced and recurrent ovarian cancer for four years. Having treated well over 100 patients, our program is one of the largest in the country. We have recently seen a surge in referrals specifically for HIPEC as a result of this new and promising data.

ABOUT THE AUTHOR

Dr. DeBernardo is a gynecologic oncologist. He established the HIPEC program for the Ob/Gyn & Women's Health Institute and has led it for four years. He is also Director of Minimally Invasive Surgery for the institute.



How do we help women choose appropriate tests and prepare for the results?

Advances in prenatal genetic tests provide pregnant women and their healthcare providers with specific medical information to inform key prenatal care decisions. While these tests can provide women with valuable information about their pregnancy, the tests can also provide information that they may not be prepared to learn about or perhaps did not want to access during their pregnancy.

Members of the obstetric healthcare team, including Ob/Gyns, certified nurse midwives, perinatologists and genetic counselors, work closely with patients to help them choose prenatal testing options that best meet patients' needs, values and goals. However, the introduction of new prenatal genetic tests and information that can be gained from their use presents unique challenges to both patients and the healthcare team.

NIPT provides a new choice

Cell-free fetal DNA screening, also known as noninvasive prenatal testing (NIPT), is a prime example. This screen provides more accurate information about the risk of conditions such as trisomies 21, 18 and 13 than is available from conventional aneuploidy screens. NIPT can also provide information about the risk of a series of other chromosomal and genetic abnormalities that previously only could

be learned using procedures such as chorionic villus sampling or amniocentesis.

How do we help pregnant patients decide whether and how to use the different prenatal screens and diagnostic tests and make choices about the pregnancy once they have that information?

The decision to use a test like NIPT is a personal one for patients. It involves the patient learning about the various conditions screened for and what the test can tell her about those conditions. Patients must decide whether and how this information aligns with their goals and needs.

Best approaches to decision-making

Informed decision-making ensures that patients and their families have the resources to make prenatal testing decisions. Autonomy is at the core of this process.

My colleagues, Josephine Johnston, LLB, and Erik Parens, PhD, at the Hastings Center,¹ and I wrote about this in a paper published in the *New England Journal of Medicine*.² We discussed the promise of such tests for patients and their families in addition to the need to implement new prenatal screens and diagnostic tests into patient care in a way that improves outcomes for women and children.





ABOUT THE AUTHOR

Dr. Farrell has a special interest in reproductive bioethics. She is Vice Chair of Clinical Research for the Ob/Gyn & Women's Health Institute.

This is just one set of questions we will have to address as we develop evidence-based and patient-centered approaches to prenatal care. These questions are a part of a line of research on medical decision-making and healthcare outcomes that I am conducting with colleagues at the Cleveland Clinic. This study, funded by the National Institutes of Health, focuses on how to best educate patients and providers about new prenatal genetic tests and, more important, how to have effective conversations that support patients' decision-making.

Our challenge in a time of flux

It is imperative that every woman has the information and support needed to make the best decisions for herself and her family. Advances in genetic technology are happening at breakneck speed, and physicians and patients can easily get caught in the middle.

Prenatal genetic counselors have traditionally played a key role in this process. However, at this time there simply are not enough genetic counselors to meet the needs of all patients considering prenatal testing, particularly as tests such as NIPT become readily available across the general obstetric population. Without adequate resources to learn about their testing choices, many women will find themselves on a decision pathway they may not be ready to face.

Our studies show that pregnant women want to understand the benefits and risks of prenatal tests, especially when they are considering which screen or diagnostic test to use. Patients also want reassurance that testing is optional.

Our studies also show that providers want to provide patient-centered support to patients and their families, but face many challenges in the process. It will be critical to coordinate our efforts across multiple disciplines to ensure that the decision-making and consent processes take place in a way that empowers patients without leaving them at a loss for how to make the best choice about their testing options.

We need to work together

Healthcare providers, policy makers and researchers need to work together in this innovative time in the delivery of prenatal care.

This presents new and exciting opportunities for us to collaborate and find solutions for evidence-based, patient-centered care in a time when genomics and precision medicine are changing how we think about healthcare.

References

1. The Hastings Center, founded in 1969, is a renowned bioethics research institute located in the Hudson Valley, north of New York City.
2. Johnston J, Farrell RM, Parens E. Supporting women's autonomy in prenatal testing. *N Engl J Med.* 2017;377(6):505-507.

Zika Infection Still Poses Concern for Pregnant Women

Here's how to manage Zika in your practice

Dr. Goje: Our knowledge about Zika has grown in the past two years, but there's still a lot to learn. We're researching, we have trials and providers need education.

Dr. Gordon: Zika is on our radar screens now, especially for pregnant women. The burden of infection for the unborn baby as well as congenital birth defects are of major concern.

Dr. Goje: How did Zika get to the United States?

Dr. Gordon: It is primarily a mosquito-borne disease, but Zika also can be transmitted sexually, through infected semen from a male who harbors the virus but is asymptomatic.

Viral RNA has been detected in semen up to six months after exposure. So couples need to practice safe sex for about six months after a partner may have been exposed.

That's generally how a pregnant woman in, say, Cleveland, Ohio, who's never traveled outside the United States, is still potentially at risk for acquisition of Zika.

Dr. Goje: The photos of babies with microcephaly in Brazil break our hearts. We know that congenital Zika syndrome includes microcephaly, brain calcifications, hearing loss and/or ophthalmic abnormalities.

Dr. Gordon: A number of studies show that Zika infection during pregnancy is clearly a risk factor for microcephaly. As we study children born to mothers with Zika, we are finding the other birth defects as well. This does not prove Zika is the



Experts **Oluwatosin Goje, MD**, head of the Ob/Gyn & Women's Health Institute Gynecologic Infectious Diseases Program, and **Steven Gordon, MD**, Chair, Department of Infectious Disease, shed light on new thinking for assessment, testing and prevention of Zika in women who are pregnant or who may become pregnant.

cause, but the numbers are statistically important and fulfill Koch's postulates.

Dr. Goje: What are the signs and symptoms of Zika virus infection?

Dr. Gordon: Most patients are asymptomatic, and that is why the Centers for Disease Control and Prevention (CDC) recommends "opting in," meaning any pregnant woman or woman who may become pregnant should be assessed based on history for risk of Zika infection.

It's not just where you've been, but also where your partner has been. Practitioners need to take a risk history for exposure for the pregnant woman and for her partner. As of July 2017, the World Health Organization (WHO) identified about 95 countries with ongoing Zika transmission.

Screening differs from testing

Dr. Goje: How is a Zika diagnosis confirmed?

Dr. Gordon: Patients don't come in with the diagnosis flashing on their forehead. The history and physical are important as is staying up to date. Diagnosis can be difficult because, unlike HIV or hepatitis C, the virus remains in tissue for a relatively short time, and women are not necessarily tested then, making diagnosis problematic.

Dr. Goje: Screening is different than testing. Who should be tested?

Dr. Gordon: The testing algorithm from the CDC and WHO continues to evolve. Today, the symptomatic pregnant woman with exposure will always be tested. But the asymptomatic pregnant woman who

may have been exposed but is not in an area of ongoing exposure doesn't necessarily have to be tested.

Nucleic acid amplification testing allows us to test for Zika virus in blood or urine up to 12 weeks after conception or exposure.

Help pregnant women avoid test anxiety

Dr. Goje: Some women and their providers will be apprehensive about not being tested.

They want to protect their baby and be sure they are infection-free. This is when education comes in because testing actually could create more anxiety.

We had a patient fly here from Florida for a second opinion because she was about to terminate a pregnancy. We reached out to the CDC to help clarify what testing would mean for her.

Dr. Gordon: You've taught me how important it is to avoid test anxiety in a pregnant woman. And that's not just for Zika, but also for screening for congenital toxoplasmosis or other congenital infections.

Dr. Goje: Correct. We don't want to create more anxiety, but we don't want to miss something important. Again, I tell providers to reach out to the CDC.

What about prevention?

Dr. Gordon: For travelers going from a non-endemic area to one where there's risk, as an obstetrician, you can certainly tell your patient not to go. Having said that, there may be reasons someone needs to go — a funeral or another occasion that

is extremely urgent. If a woman who is pregnant or potentially pregnant must go, then we talk about nonpharmacologic interventions, or mosquito avoidance. Avoiding times of the day when mosquitoes bite frequently, wearing long sleeves and covering up, using an FDA-approved mosquito repellent and netting, staying in shelters with screens and air conditioning are all good. These are not foolproof measures, of course.

Dr. Goje: So it is about mitigating risk.

Dr. Gordon: Yes. One thing you taught me is that about 1 percent of the world's population is pregnant at any given time. This reminds us that society really does adore this vulnerable population and should protect and cocoon them. It's all about putting our patients first no matter where they are.

Is natural immunity possible?

Dr. Goje: Patients have asked me if they may be immune if they have been exposed to Zika. I had a patient jokingly ask if she should expose herself to Zika, then get married and have babies!

Dr. Gordon: Don't do that! We are not at the point when we can say go get a natural infection. I do believe basic science will bring us primary vaccine prevention, an antiviral, as well as a vaccine for women and men who are in areas with ongoing transmission. So stay tuned.

Dr. Goje: Thank you, Dr. Gordon. If physicians have questions, please reach out to the CDC, Ohio Department of Health or the Infectious Disease Department at Cleveland Clinic.

Unlocking the Mysteries of Ovarian Tissue Freezing and Transplantation

By Rebecca Flyckt, MD

Research examines vitrification, follicular viability, reimplantation

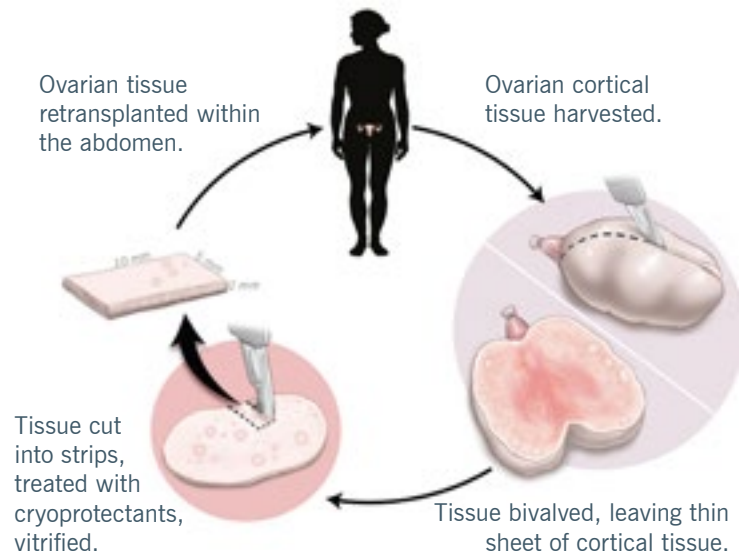
Although many women with cancer are living longer, healthier lives thanks to improved treatment options, the diagnosis of cancer still causes many worries for patients. A common concern for women and girls with a new cancer diagnosis is whether future childbearing will be difficult or even impossible after treatment. Treatments that cure malignancy can also damage the ovaries in a way that results in menstrual dysfunction, infertility or premature menopause. Perhaps the most at-risk population is prepubertal girls with cancer, who are not eligible to pursue gold-standard fertility-preserving strategies like egg and embryo freezing.

Ovarian tissue freezing

For this population and for women who cannot or prefer not to undergo egg or embryo freezing, Cleveland Clinic offers ovarian tissue freezing. The American Society of Reproductive Medicine still considers ovarian tissue freezing to be experimental in humans, and this procedure can be performed only under an institutional review board-approved protocol with detailed informed consent. To date, close to 100 live births using this technique have been reported worldwide. Cleveland Clinic offers ovarian tissue freezing for pediatric and adult populations, and tissue freezing has now been performed for dozens of women and girls at our institution.

Ovarian tissue freezing involves harvesting ovarian cortical tissue using outpatient laparoscopic techniques. This method allows rapid recovery and no delay in chemotherapy or radiation. Once the patient has recovered from cancer treatment and is ready to pursue fertility, the tissue can be retransplanted using fine sutures to secure the strips of ovary in position within the abdomen. Transplantation may not occur until decades after the original freezing procedure. Pregnancies can then be conceived either spontaneously or with the help of fertility treatments.

Ovarian Tissue Freezing



Tissue freezing research using sheep model

Because ovarian tissue freezing and transplantation are still experimental, research is underway to optimize the technique. At Cleveland Clinic, a trial with sheep models is beginning to answer important questions in ovarian tissue freezing. For example, most in vitro fertilization programs use vitrification (a rapid freezing technique) to freeze eggs and embryos, due to superior pregnancy and live birth rates. However, most live births using ovarian tissue have been obtained using a slow freezing technique, potentially because vitrification was not widely available previously. Therefore, an important debate in fertility preservation research is whether slow freezing or vitrification yields better results for ovarian tissue.

In this Cleveland Clinic trial, portions of ovary from the same sheep are frozen at our Fertility Center research lab using each of the two methods. The tissue is then thawed and reimplanted, and studies of follicle viability are obtained for side-by-side comparison.

A secondary objective of the study is to determine whether follicles isolated from ovarian tissue can be reimplanted using a supportive matrix. This technique may help reduce the risk of reintroducing cancer cells with implantation. This concern exists mainly for bloodborne cancers, such as leukemia, that may be found in ovarian tissue. Results from the trial are expected in 2018. We hope they will shed light on these two very important questions in fertility preservation.

ABOUT THE AUTHOR



Dr. Flyckt is an expert in reproductive medicine. She is Director of the Fertility Preservation and Cancer Program at the Ob/Gyn & Women's Health Institute.

Number of Fibroids Removed May Impact Fertility After Myomectomy

By Tommaso Falcone, MD, and Shirley Shue

Finding may alter expectations for pregnancy

Women of reproductive age with symptomatic fibroids who present to Cleveland Clinic are typically offered myomectomy rather than hysterectomy to preserve their fertility. However, myomectomy is associated with potentially extensive blood loss, particularly when multiple fibroids are removed.

Facing a dearth of good data showing that removing fibroids increases a woman's chance of becoming pregnant, Cleveland Clinic Ob/Gyn researchers undertook a study to evaluate whether the risks of myomectomy would pay off for these women. We wanted to determine whether the number of fibroids removed during myomectomy affects long-term fertility outcomes in women of reproductive age.

Fibroids are a significant public health issue, especially in the African-American community. So it is very important for us to take on the challenging research this condition requires and investigate the

impact of fibroid surgery. The study was presented at the American Society of Reproductive Medicine Scientific Congress & Expo last year.

Is 6 the magic number?

Of 605 patients ages 18-40 who had undergone myomectomy at Cleveland Clinic, 144 responded to our survey. They were categorized as having had either one to six fibroids or more than six fibroids removed.

Our findings included the following:

- African-American women were more likely than other groups to have more than six fibroids removed (58.3 versus 41.6 percent).
- Patients with more than six fibroids removed were less likely to achieve pregnancy after myomectomy than those with six or fewer fibroids removed (22.9 versus 70.8 percent).
- Compared with 17.6 percent of patients who had six or fewer fibroids removed, 45 percent of those with

more than six fibroids removed relied on fertility treatments to achieve pregnancy.

- Of those who became pregnant after having more than six fibroids removed, 45.5 percent had a term birth, 45.5 percent miscarried and 9.1 percent had an ectopic pregnancy. This compares with 61.8 percent, 23.5 percent and 13.2 percent in women who had six or fewer fibroids removed.

In summary, we found that women who have more than six fibroids removed and wish to conceive may not benefit from myomectomy to the same degree as those with six or fewer fibroids. It is unlikely this single study will change clinical practice, but it may open the door to more research.

ABOUT THE AUTHORS

Dr. Falcone is Chairman of the Ob/Gyn & Women's Health Institute. Ms. Shue is a Case Western Reserve University School of Medicine student.