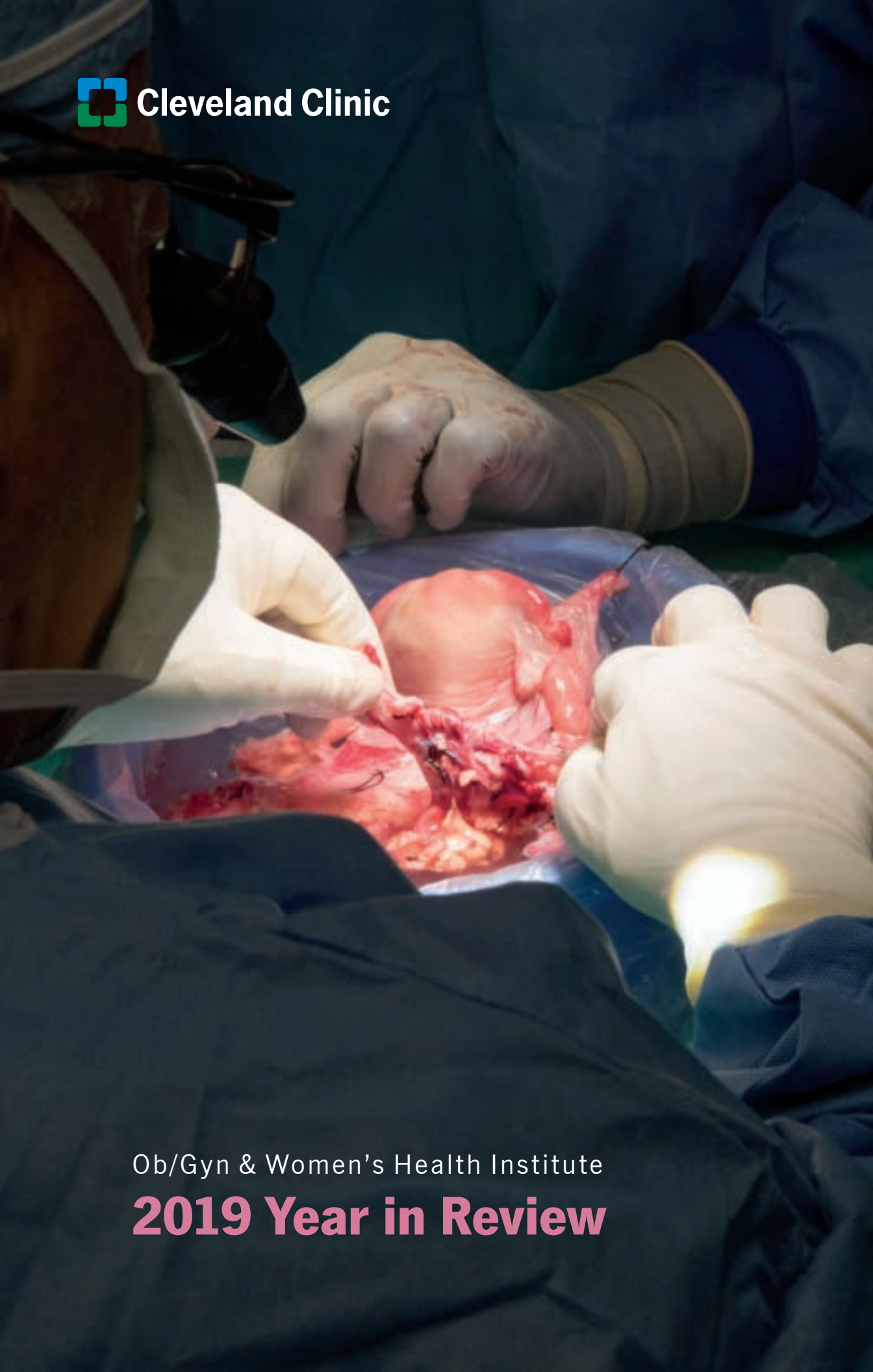

Cleveland Clinic

Ob/Gyn & Women's Health Institute

2019 Year in Review

MESSAGE FROM THE CHAIR

Dear Colleagues,

I am pleased to share the Cleveland Clinic Ob/Gyn & Women's Health Institute's *2019 Year in Review*, which highlights our efforts to advance women's health. This issue also illustrates our commitment to the tripartite mission of Cleveland Clinic: to provide better care of the sick, investigation into their problems and further education of those who serve.

2019 was a year of incredible innovation at Cleveland Clinic, including a live birth from a deceased-donor uterine transplant — a North American first — and our first several fetal surgeries. These tremendous achievements are the result of the multidisciplinary collaborations and patient-centered care that are hallmarks of Cleveland Clinic.

We continue to push the boundaries of research in gynecologic cancer, both at the bench and at the bedside, through our Center for Research Excellence in Gynecologic Cancer. Cleveland Clinic's Gynecologic Cancer Program offers patients the latest in gynecologic cancer management, including the newest drug therapies. Additionally, as a result of a generous philanthropic donation, Robert DeBernardo, MD, was named the first Laura J. Fogarty Endowed Chair in Women's Health for Uterine Cancer Research.

We have efforts underway to decrease infant and maternal mortality, including the implementation of protocols to optimize care in obstetric emergencies at all delivery sites. We are also adapting our practices to current trends in women's health, including rising rates of sexually transmitted infections.

We continue to train medical students and Ob/Gyn residents and fellows on the verge of exciting careers. Our 7-year-old Ob/Gyn residency program is the only one in the country with a tracking curriculum, allowing residents to customize their studies according to their subspecialty interests.

As leaders in women's health, we continue to share knowledge with colleagues around the world through courses and lectures presented at Cleveland Clinic and at national and international medical meetings. Notably, Marie Fidela Paraiso, MD, Head of the Section for Urogynecology and Reconstructive Pelvic Surgery, served as the 2019 President of the American Association of Gynecologic Laparoscopists (AAGL). Also in 2019, Linda Bradley, MD, Director of Hysteroscopic Services and Vice Chair for Diversity and Inclusion, began a four-year term as Medical Director of AAGL.

I applaud our team's exceptional work in patient care, research and education, and invite you to read more about it in these pages. I encourage you to reach out with questions and feedback.

Sincerely,

Beri Ridgeway, MD

Chair, Ob/Gyn & Women's Health Institute

216.444.6601 | ridgewb@ccf.org | @beridgeway

On the cover: Andreas Tzakis, MD, PhD, harvests the uterus from a deceased donor.


Ridgeway, M
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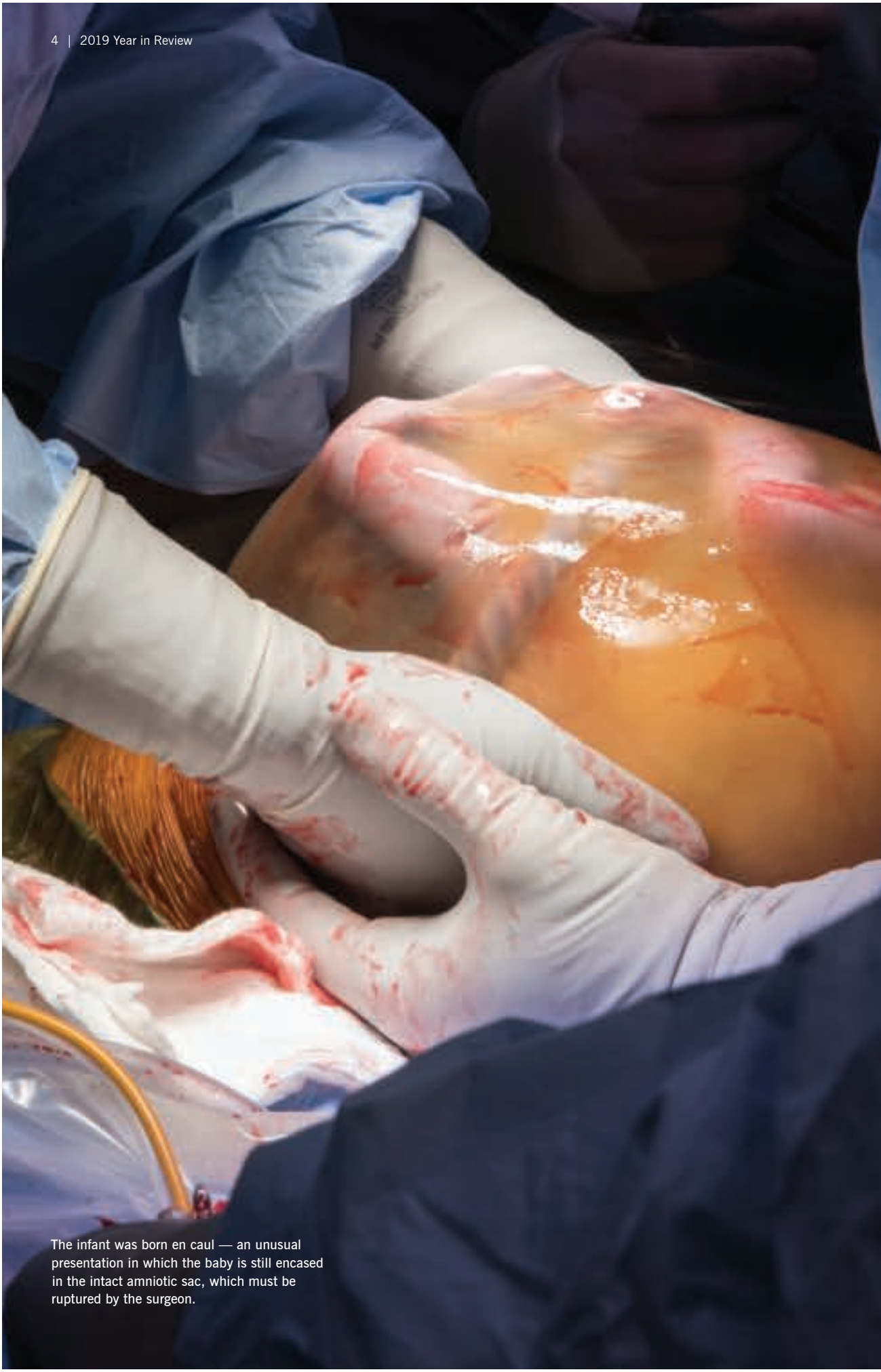

The infant was born en caul — an unusual presentation in which the baby is still encased in the intact amniotic sac, which must be ruptured by the surgeon.

Live Birth from Deceased-Donor Uterine Transplant at Cleveland Clinic

Procedure expands options for women with uterine factor infertility

In a first for North America, a Cleveland Clinic patient has given birth after receiving a transplanted uterus from a deceased donor.

The transplant was performed in 2017. In late 2018, the mother, who is in her mid-30s, became pregnant through in vitro fertilization. The delivery via caesarean section took place in June 2019. The mother and her daughter are doing well.

The birth is the culmination of years of research and preparation by Cleveland Clinic's multidisciplinary uterine transplant team, which includes specialists in transplant surgery, Ob/Gyn, fertility, neonatology, bioethics, psychiatry, nursing, anesthesiology, infectious disease, interventional radiology, patient advocacy and social work.

Although the transplant is still experimental, its success helps validate a new therapeutic option for women of reproductive age with absolute uterine factor infertility when a living donor is unavailable.

"Through our research, we are working to make uterine transplantation a reality for women who choose this approach," says transplant surgeon Andreas Tzakis, MD, PhD, who has spearheaded Cleveland Clinic's efforts to develop and advance the procedure. "This case confirms that the birth of a healthy baby is perfectly feasible after a uterine transplant from a deceased donor."

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When it came time for caesarean delivery, the entire team was present. Cleveland Clinic maternal-fetal medicine specialist Uma Perni, MD, who managed the patient's prenatal care, led the procedure. The infant was born en caul — an unusual presentation in which the baby is still encased in the intact amniotic sac, which must be ruptured by the surgeon. Seeing the child appear was an emotional peak.

"The teamwork it took to make this happen for our patient was remarkable. I am so proud," says Tommaso Falcone, MD, Chief of Staff and Chief Academic Officer at Cleveland Clinic London. "This clinical trial reflects the Cleveland Clinic tradition of innovation in clinical medicine."

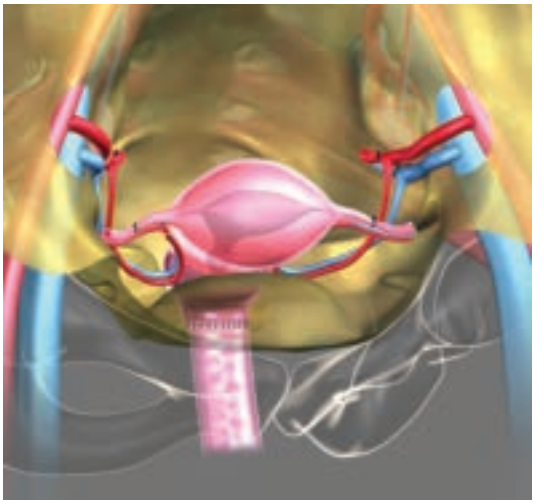
"We couldn't have asked for a better outcome," says Dr. Perni. "The field of uterus transplantation is rapidly evolving, and it is exciting to see what the options may be for women in the future."

Expanding the frontiers of infertility treatment

Deceased-donor transplantation has the potential to increase overall organ supply and patient access to the procedure while avoiding exposing a living donor to prolonged surgery and extensive pelvic dissection. "There are pros and cons for both the living and deceased-donor approaches," Dr. Tzakis says. The surgery to obtain the donor uterus "is quite involved, and we were concerned about complications" in a living patient. "We decided to use deceased donors."

Using an organ from a deceased donor, Cleveland Clinic's team performed the nation's first uterine transplant on Feb. 24, 2016, as part of a clinical trial of the procedure. A vascular *Candida* infection caused complications that necessitated removal of the transplanted uterus 12 days after the surgery. Following an extensive review and revision of the transplant program's protocols, the Cleveland Clinic team resumed the trial of the deceased-donor procedure in 2017.

The trial continues. To date, the program has undertaken a total of five transplants. Three were successful engrafts: One of those resulted in last month's birth, and two are pending embryo transfer after in vitro fertilization. The remaining two transplants ended with hysterectomies.



A total of 10 patients eventually will undergo transplantation during the trial, allowing Cleveland Clinic researchers to gather data intended to help refine and improve patient selection and the surgery, recovery, immunosuppression, in vitro fertilization and delivery processes.

Participation in the clinical trial requires that candidates between the ages of 21 and 45 be intensively screened and evaluated by a multidisciplinary team to ensure that each woman is medically suitable, understands the potential consequences of the procedure, and has the personality, social support and other prerequisites for a successful outcome. Patients who are selected for the clinical trial must first undergo in vitro fertilization (IVF) and cryopreservation of at least six embryos harvested by a team of IVF specialists. That is followed by a wait for a matching deceased donor (a woman of reproductive age who has previously given birth), the transplant surgery, immunosuppression and infection prophylaxis, embryo transfer, caesarean delivery, and eventual hysterectomy to remove the graft after one or two pregnancies.

The infant's birth is the culmination of years of research and preparation.

Intrauterine Myelomeningocele Repair Reduces Neurological Damage in the Tiniest Patients

First cases set the course for a full spectrum of intrauterine therapies

Led by one of the world's most experienced fetal surgeons, Darrell Cass, MD, the first intrauterine myelomeningocele (MMC) repairs in Northern Ohio were performed at Cleveland Clinic.

MMC, or open spina bifida, is the most common congenital central nervous system defect, occurring in approximately 1,645 births annually in the United States.[1] The condition develops in the first four weeks after conception and is characterized by incomplete neural tube closure and a fluid-filled sac containing an exposed, extruded segment of spinal cord and nerves. With the closure of their neural tube defects, these tiny patients' Arnold-Chiari malformations are reversed, thus decreasing the risk for hydrocephalus and the need for shunting.

Innovations enable earlier intervention for developing fetus

Historically, MMC lesions were surgically closed after delivery, limiting the prevention of neurologic loss. As prenatal diagnostic capabilities and technology (particularly ultrasonography and magnetic resonance imaging) improved, MMC could be detected and characterized as early as the first trimester, raising the prospect of fetal surgical repair.

"By successfully repairing [the defect] before birth, we are limiting the ongoing damage to the spinal cord from the intra-amniotic environment," explains Dr. Cass. "In ultrasound studies of fetuses with spina bifida, we can witness them doing functions with their legs and ankles that are lost later in the pregnancy."

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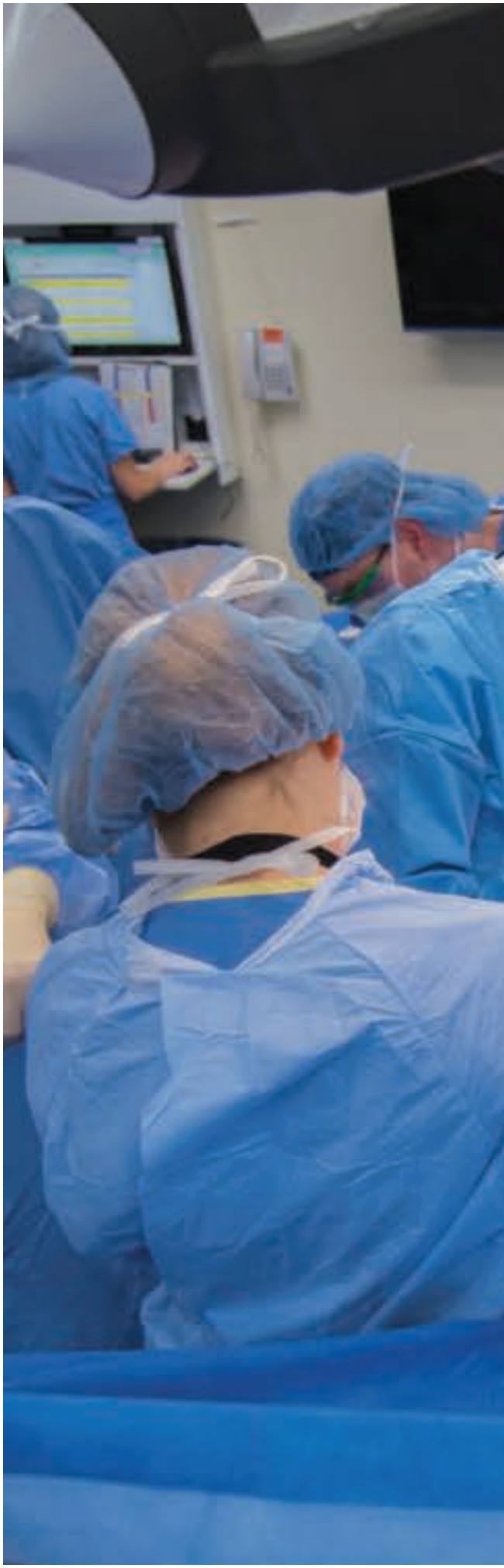

Pediatric neurosurgeons Violette Recinos, MD (left, wearing head-mounted camera), and Kaine Onwuzulike, MD, PhD, repair the myelomeningocele lesion.

Amanda Kalan, MD (left), places sutures to secure the membranes at the start of the hysterotomy.

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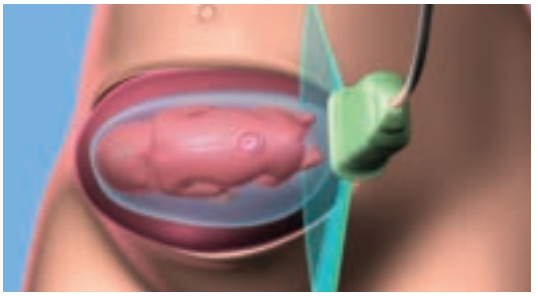
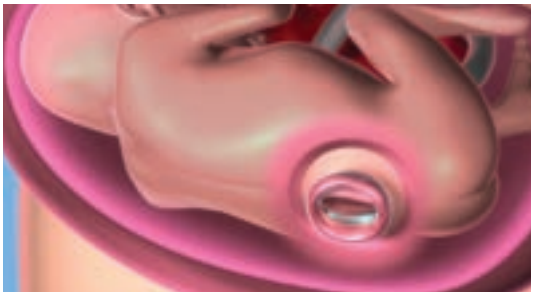
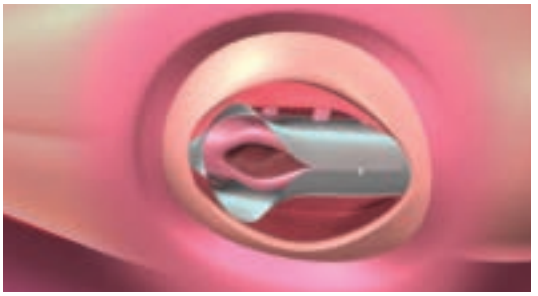
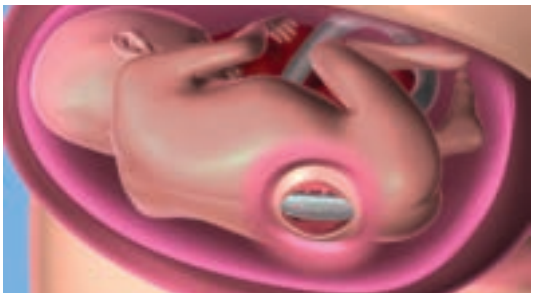
Closing the lesion

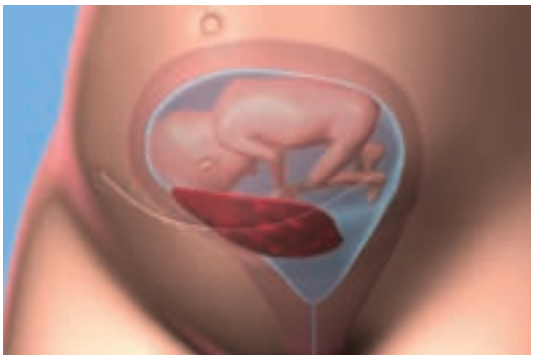
In the first MMC procedure, Dr. Cass and Amanda Kalan, MD, used ultrasound to be certain of the exact location and lie of the fetus within the uterus, ensuring that the uterine incision they were about to make was optimal to access the fetus's MMC lesion while avoiding the placenta. Dr. Cass made a 4.5-centimeter uterine incision, using staples to control bleeding and infusing warm Ringer's lactate to maintain uterine volume and fetal temperature. Pediatric neurosurgeons Kaine Onwuzulike, MD, PhD, and Violette Recinos, MD, then performed a multilayer closure of the MMC lesion. They dissected the placode to release it from the arachnoid membrane, allowing it to retract into the spinal canal, and then mobilized and sutured the myofascia, dura and skin. Dr. Cass closed the hysterotomy, re-placed the uterus into the mother's abdomen and closed the laparotomy incision. Tocolytics were infused intravenously to suppress preterm labor.











A great start and a look ahead

Dr. Cass has high praise for his colleagues in the team's first fetal surgery efforts together.

"It's as good an outcome as we can see anywhere in the world," he says. "Our anesthesiologists were the best I've worked with — cool and confident. Dr. Kalan and the others in maternal-fetal medicine are amazing to work with. Dr. Erenberg (Francine Erenberg, MD), did a great job monitoring the baby to make sure nothing went wrong. The repair that our neurosurgeons did was the best I've seen, and it was brand-new for them. And the nurses, care coordinators and operative team were incredibly dedicated, enthusiastic, well prepared and attentive."

The next steps are to prepare for additional and more complex cases, Dr. Cass says, and to make sure potential patients and referring physicians are aware that full-spectrum fetal surgery is now available in the region.

Reference:

[1]Williams J, Mai CT, Mulinare J, et al. Updated estimates of neural tube defects prevented by mandatory folic acid fortification – United States, 1995-2011. *MMWR Morb Mortal Wkly Rep*. 2015;64(1):1-5.

Maternal Mortality: Reducing Disparities

Cleveland Clinic efforts to improve access, prevention and emergency management

In the United States, there are significant racial disparities in pregnancy-related mortality, according to 2016 data collected in the Centers for Disease Control and Prevention's Pregnancy Mortality Surveillance System.[1] Black, non-Hispanic women were 3.2 times more likely to die from a pregnancy-related death than white women, with pregnancy-related mortality rates (PRMR) of 42.4 and 13.0 per 100,000 live births among the black, non-Hispanic and the white, non-Hispanic populations, respectively.

PRMR was also significantly higher for women living in metropolitan or rural counties, those who are unmarried, and those over the age of 30. Leading causes of death include hemorrhage, cardiomyopathy, infection and other cardiovascular conditions, as well as other, noncardiovascular-related medical conditions.

Social determinants of health

"It's very important to recognize that these disparities are related to social determinants of health along with purely biological factors," states Jeff Chapa, MD, a maternal-fetal medicine specialist. "We're addressing these issues in a number of ways. We are improving access at different locations throughout the community, including the Cleveland Clinic Stephanie Tubbs Jones Health Center, Lakewood Family Health Center and Marymount Hospital, and we now offer high-risk maternal-fetal medicine services at Cleveland Clinic main campus. We have also implemented earlier postpartum checks, at one week postpartum for patients at high risk and at two weeks postpartum for others. Patients are also educated to watch for symptoms and come in earlier if they have concerns. We are partnering with public health programs such as CenteringPregnancy® and First Year Cleveland."

Optimizing management of obstetric emergencies

Additional efforts underway to decrease preventable maternal morbidity and mortality, says maternal-fetal medicine specialist Kathleen Berkowitz, MD, include the implementation of order sets and protocols to optimize the management of the three main causes of obstetrics emergencies: obstetric hemorrhage, preeclampsia and hypertensive disorders, and deep vein thrombosis (DVT).

"With nearly 10,000 deliveries per year in Cleveland Clinic hospitals, obstetric hemorrhage is a near daily occurrence," Dr. Berkowitz says. "Everyone who will be involved in care on the antepartum, labor and delivery, or postpartum floors is involved in obstetric hemorrhage simulations. In 2019, we also built automatic order sets for the de-escalation of high blood pressure. The order is triggered when a patient hits a threshold for high blood pressure, and calls for medication administration within 60 minutes or less. Finally, we have DVT-related protocols that ensure all our patients are treated with either mechanical or chemical prophylaxis according to individual patient risk factors."

"As a healthcare system, we are doing everything possible to develop solutions to maternal morbidity and mortality. Once we have successfully scaled these initiatives, we intend to partner with the greater Cleveland community, and hope to serve as a model for other Cuyahoga County-area hospitals. We want to do more than just prevent maternal deaths locally; we want to see PRMR decrease throughout the state of Ohio," Dr. Berkowitz notes.

Reference:

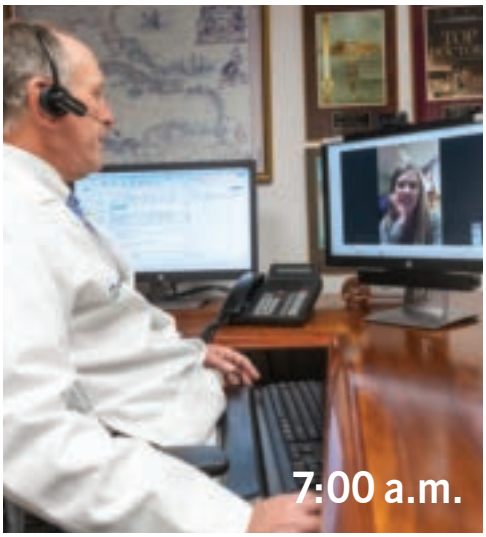
[1] Centers for Disease Control and Prevention. Pregnancy Mortality Surveillance System. https://www.cdc.gov/reproductivehealth/maternal-mortality/pregnancy-mortality-surveillance-system.htm. Accessed Nov. 11, 2019.

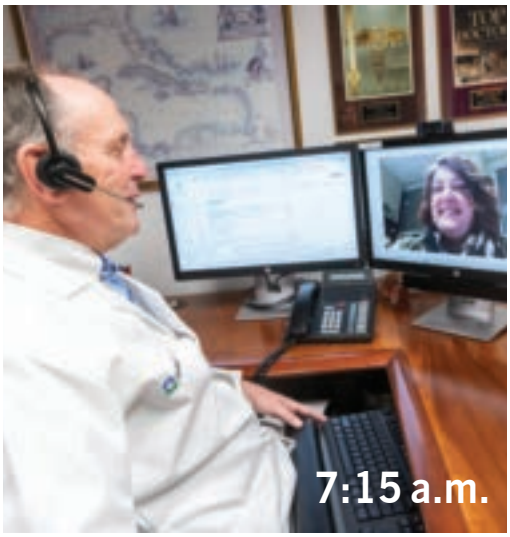

Cleveland Clinic

Virtual OB Visits: A Hybrid Option for Low-Risk Patients

How I built a hybrid in-office and virtual practice with a focus on access and patient experience

By Julian Peskin, MD, MBA





Full disclosure: I love virtual visits

Contrary to what some may think, sometimes I find them more intimate than an office visit. I get to see the patients in their homes, and share in their surprise when the cat jumps up on the table or a small child runs by wearing nothing but a diaper. Patients love them too — it can be difficult to juggle the demands of work or find childcare, and then sit in traffic and fight for a parking space for an appointment that might last 15 minutes.

One of the reasons virtual visits work well in obstetrics is that we have the opportunity to develop relationships with women over the nine to 12 months they are in our care. This means our patients have time to get to know and trust us, and we are able to pick up on subtle cues or changes online just as we are in the office.

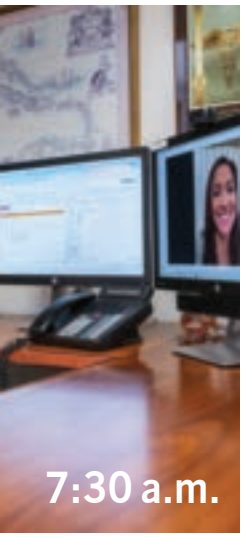
I have had the opportunity to complete about 160 pregnancies using a hybrid model of office-based and virtual care. In this article, I explain my process, including when and how virtual obstetrics visits are scheduled, and what takes place during the visit itself.

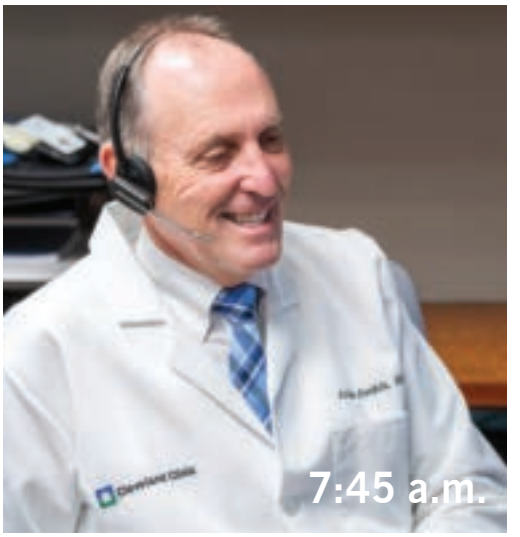
Plant the seed early

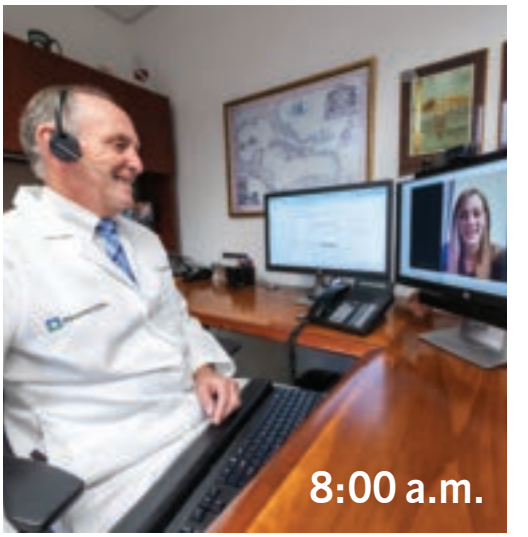
When I see patients at their first visits, I plant the seed of what a virtual visit entails. I say to them: "Virtual visits are a little like FaceTime®. Throughout the course of your pregnancy, you'll see me maybe 13 or 14 times. Rather than taking time away from work, or finding childcare, and driving all this way, we can usually convert two or three visits into virtual visits."

Schedule multiple visits at one time

With my patients, I average about three virtual visits per pregnancy, built around the instances in which I know an office visit will be required. Generally speaking, these virtual visits take place in weeks 22, 26 and 32. If I decide virtual visits are appropriate, patients will leave my office after their 16-week visit with a Doppler ultrasound device and a blood pressure cuff.







Blocks of virtual time

The waiting room is one significant difference between in-office and virtual care: If you are running behind in the office, patients see that your waiting room is full. They know you are in the office, and your support staff can offer reassurance. Online, however, a patient doesn't really see anything until the appointment begins. They might wait a few minutes past their appointment time and then drop off. I like to block portions of my clinic schedule for virtual visits. This simplifies the scheduling process and keeps me on time.

Develop hybrid options and stay agile

Virtual visits are not appropriate for all patients. Patients whose pregnancies are complicated by hypertension or multiples or who are at high risk for preterm labor should be managed in the office. Additionally, anxious patients don't do well with virtual visits, in my experience. If any of these complications arise, I'm honest with my patients. For other patients, I might swap out more than three office visits.

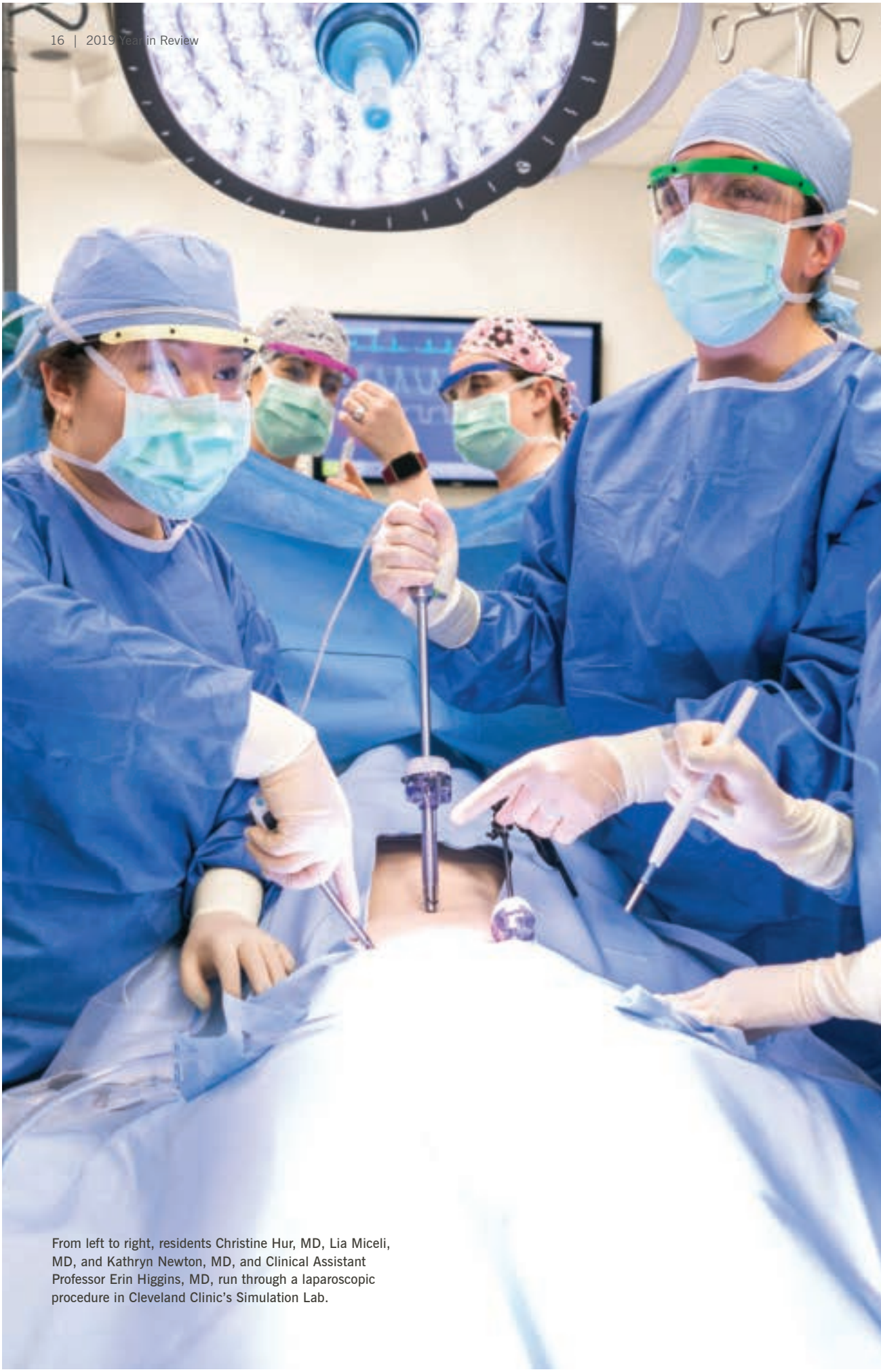
Provide the same care you would if the patient were in the office

The care I provide virtually should be identical to the care I provide in the office — there is no trade-off between convenience and the quality of patient care.

Patients are instructed to measure their weight and blood pressure and listen to the heartbeat before each appointment. I ask some preliminary questions, such as: "Is the baby moving? Do you have any complaints? Are you bleeding?" Then I ask my patient to give me the weight, blood pressure and heartbeat metrics. Otherwise, I manage the visit just as I would a face-to-face visit. We discuss upcoming tests and scans, any birth plans, and whether they have a pediatrician lined up.

Expand thoughtfully

As we look to expand our offerings to increase access and convenience for our patients, it is important to keep patient safety in mind. For now, in obstetrics, we stick to the lower risk patients.



From left to right, residents Christine Hur, MD, Lia Miceli, MD, and Kathryn Newton, MD, and Clinical Assistant Professor Erin Higgins, MD, run through a laparoscopic procedure in Cleveland Clinic's Simulation Lab.

Simulation in Obstetrics and Gynecology

Multiple teaching modalities improve procedural and communication skills

By Erin Higgins, MD, Cara King, DO, and Vicki Reed, MD

Simulation itself is nothing new in obstetrics and gynecology. In fact, as a learning modality, simulation has a rich history spanning several centuries. However, advances in computing and electronics in the recent past have led to the development of high-tech mannequins that simulate interactions with patients. These advances, combined with decreasing work hours and an ever-increasing list of procedures to learn have contributed to the integration of simulation into undergraduate and graduate medical education.

Simulation is essentially any skills practice outside of patient care. Lower-fidelity simulations might be as simple as learning how to suture on a suture board. Skills-based simulation training also allows learners to practice procedures such as laparoscopy, endometrial or vulvar biopsies, and forceps delivery. Larger, team-based drills can simulate high-acuity, low-frequency events in Ob/Gyn surgery, such as a maternal code, eclampsia and intraoperative hemorrhage.

Low-fidelity simulation for skill development

While high-fidelity models are great at simulating real-world situations, they aren't always necessary to teach procedural skills. Attaining these skills requires a lot of practice, and in the early stages of training, we wouldn't want medical students or residents to hone these skills using patients. Instead, we use everything from pig feet and citrus fruit to board games to handmade vaginal cuff models crafted from corduroy and neoprene. There's no fancy artificial intelligence involved in these low-fidelity simulation models; nevertheless, they give learners the opportunity to practice throwing knots, for example, before they get into the operating room.

High-fidelity simulation focuses on teamwork and communication skills

In order to give learners of all levels (i.e., medical students, residents, fellows, attending physicians and nurses) experience in high-acuity, low-frequency Ob/Gyn surgical emergencies, we conduct high-fidelity simulations. These can be fully automated, often taking place in a simulated operating room or birthing room. Educators, separated from the simulation by a two-way mirror, are able to speak for the mannequin and control every vital sign. The mannequin has a detectable pulse and breath sounds. It can deliver a baby. Tubing can even be set up so that the mannequin can "bleed" or leak fluids. These simulated emergencies involve the entire multidisciplinary care team and give everyone a chance to develop the teamwork skills (e.g., conducting closed-loop communication and delegating tasks) necessary in an emergency without sacrificing patient safety.

Developing a simulated learning experience

These scenarios are time and labor-intensive. After defining our learning objectives, we develop the patient presentation, write a script for what will happen based on the learner's actions, and work with education specialists in Cleveland Clinic's Simulation and Advanced Skills Center to ensure the materials we need will be available.

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For learners, there are typically four steps in simulated learning:

- The prereading, where learners study literature related to the topic or skill.
- The prebrief, which includes team introductions, reviewing the learning objectives and reducing performance anxiety. We assure learners that this is a safe and confidential learning environment, and encourage them to treat the simulation as if it were a real-life scenario.
- The simulation, with learners in the delivery or operating room working on simulated patients, while educators manipulate and observe from the control room.
- The debrief, which includes discussion about what went well and opportunities for improvement and is generally four to five times longer than the simulation itself.

Simulation can be an exciting, affordable, standardized and effective way to educate caregivers in Ob/Gyn while promoting patient safety through communication and teamwork. With a wide range of teaching modalities, every interaction and procedure a learner might undertake with a patient can be simulated in some fashion, whether in a lab or with a standardized patient.

Posterior Repair May Improve Outcomes with Sacrocolpopexy

Asymptomatic rectoceles may become symptomatic after sacrocolpopexy

Women with vaginal prolapse often also have rectoceles because of defects in their posterior vaginal wall. Even if the rectoceles are asymptomatic, repairing them at the time of sacrocolpopexy may reduce the odds of prolapse recurrence, according to a recent study.[1]

"Currently, there is no standard regarding whether a posterior repair or any level III pelvic organ prolapse support procedures are needed at time of sacrocolpopexy," says Olivia Chang, MD, MPH, a fellow in the Cleveland Clinic Section of Urogynecology and Pelvic Reconstructive Surgery and first author on the study.

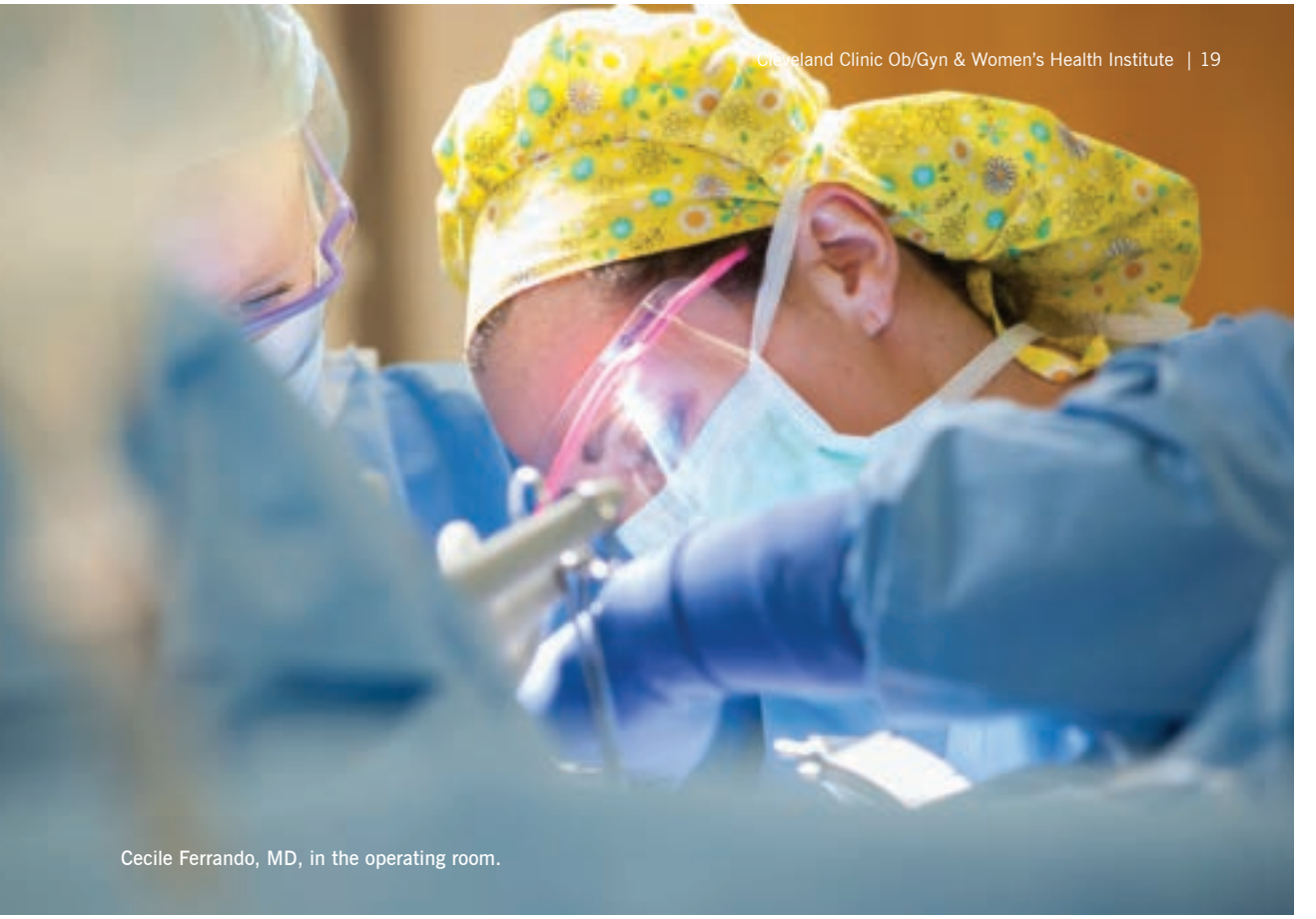
"There are two trains of thought," Dr. Chang continues. "Some people think that repair is needed to provide level III pelvic organ support. Others believe repair may actually cause more harm by leading to dyspareunia and defecatory dysfunction. We wanted to see if posterior repair actually reduces prolapse recurrence."

Asymptomatic rectoceles

The study included a retrospective chart review and prospective follow-up survey of 709 patients who underwent laparoscopic, robotic or abdominal sacrocolpopexy at a tertiary care center from 2004 to 2014. The study included patients with asymptomatic rectoceles.

"We focused on patients who have rectocele but no constipation, dyschezia, excessive straining or splinting, because some physicians may do posterior repair for those symptoms," says Dr. Chang.

In patients with asymptomatic rectoceles, 185 (54%) had sacrocolpopexy only and 159 (46.2%) had sacrocolpopexy plus a concurrent posterior



Cecile Ferrando, MD, in the operating room.

repair. The women who had sacrocolpopexy only were older (60.6 versus 56.9 years) and more likely to have had a prior relapse repair (46.0% versus 20.3%).

"We used a composite patient-centered outcome as our primary outcome. We included subjective bulge symptoms and retreatment. We found a higher rate of composite failure in patients who had only sacrocolpopexy. On regression analysis, the odds of having a failure were 2.79 times higher in patients who had sacrocolpopexy alone compared with those who had sacrocolpopexy combined with a posterior repair," says Dr. Chang.

Composite failure lower in sacrocolpopexy with concurrent posterior repair

In both groups, the composite failure rate was 10.2%. A significantly higher percentage of patients in the group that had sacrocolpopexy alone had composite failure (13.5%) than in the group that had sacrocolpopexy plus a concurrent posterior repair (6.3%). In both groups, incidence of new defecatory dysfunction following surgery was low (5.6% for sacrocolpopexy alone versus 7.5% for sacrocolpopexy plus concurrent posterior repair).

"A lot of literature suggests that a posterior repair may cause sexual dysfunction or defecatory dysfunction. We were surprised that we did not find that in our population," says Cecile Ferrando, MD, MPH, Associate Program Director of Cleveland Clinic's Female Pelvic Medicine and Reconstructive Surgery Fellowship program and Director of Cleveland Clinic's Transgender Surgery and Medicine program. "Based on our results, this suggests that a posterior repair at the time of sacrocolpopexy can reduce prolapse recurrence in women who are asymptomatic. However, patients and surgeons must make a joint decision in weighing the risks of prolapse recurrence with the development of possible dyspareunia and defecatory dysfunction. A very interesting new direction for research in this area would be a prospective, randomized controlled trial comparing posterior repair with no posterior repair at the time of sacrocolpopexy in asymptomatic patients."

Reference:

[1] Chang OH, Davidson ER, Thomas T, Paraiso MF, Ferrando CA. Does concurrent posterior repair for the asymptomatic rectocele reduce prolapse recurrence after sacrocolpopexy? *Female Pelvic Med & Reconstr Surg*. 2019;25(5S):S184-S327.


Clinic

FDA Orders Transvaginal Mesh Manufacturers to Stop Sale and Distribution

By Marie Fidela Paraiso, MD

As President of the American Association of Gynecologic Laparoscopists (AAGL), I have been fielding calls about the announcement from the U.S. Food and Drug Administration (FDA), which ordered manufacturers to cease their sale and distribution of transvaginal mesh used for the treatment of pelvic organ prolapse (POP).

An important distinction

There's an important distinction to make here: The FDA has ordered Boston Scientific and Coloplast to stop selling surgical mesh for some — but not all — procedures related to pelvic floor disorders. Some media sources have not conveyed that subtlety.

The mesh itself is not defective. The FDA changes apply to mesh used in transvaginal repair of POP. The FDA's decision does not apply to mesh that is inserted through an abdominal incision (open, laparoscopic or robotic) for POP repair, or to mesh used in midurethral sling procedures for the treatment of stress urinary incontinence.

Transvaginal mesh is not necessarily inferior

I am co-author of a recently published manuscript in the *Journal of the American Medical Association* from the Pelvic Floor Disorders Network with data indicating that the transvaginal mesh procedure is not inferior to native tissue procedures.[1] However, the FDA's mandate is that researchers prove the mesh procedure to be superior to native tissue repair.

In my experience with the most widely used transvaginal mesh procedure since 2007, it has not been associated with increased complications compared with native tissue repair. There are patients for whom we believe transvaginal mesh procedures are beneficial, especially women who have had previous failed vaginal procedures, recurrent prolapse, or patients for whom an additional abdominal procedure may be contraindicated.

Our research shows that transvaginal mesh procedures for pelvic organ prolapse are very time efficient. Following the FDA mandate, we are relegated to treating POP with native tissue repairs by vaginal, or abdominal route (open, laparoscopic or robotic) mesh repairs with sacrocolpopexy. These procedures are very good, but they may not work for or be indicated in everyone.

Mesh remains the gold-standard treatment for stress urinary incontinence and abdominal mesh repairs for vaginal vault prolapse. Medical consensus right now is that sling mesh for incontinence is one of the best and safest treatments for urinary incontinence. Additionally, there is sufficient evidence to support the use of mesh repair for vaginal vault prolapse with sacrocolpopexy.

Next steps

There are alternative therapies we can offer patients, including native tissue repair and abdominal route mesh repair.

Patients with mesh in place who are not experiencing symptoms of pelvic pain, pain with intercourse, or persistent, abnormal vaginal discharge or bleeding as a result of vaginal mesh exposure should not worry at the present time. They should maintain the follow-up schedule, and contact their physician's office if anything changes.

Reference:

[1]Nager CW, Visco AG, Richter HE, et al. Effect of vaginal mesh hysteropexy vs vaginal hysterectomy with uterosacral ligament suspension on treatment failure in women with uterovaginal prolapse: a randomized clinical trial. *JAMA*. 2018;322(11):292-293.

Coordinated Efforts for Research in Gynecologic Cancers

Gynecologic cancers are a leading cause of cancer-related deaths in women. The ability of gynecologic tumors to adapt to and evade treatment is a major factor contributing to the poor outcomes that many patients face. Cleveland Clinic has taken steps to develop and deliver the care that patients with gynecologic cancers need, forming the Center for Research Excellence in Gynecologic Cancer (CREGC) and, thanks to a generous philanthropic gift, naming the first Laura J. Fogarty Endowed Chair in Women's Health for Uterine Cancer Research.

Breakthrough research opportunities

The CREGC is a comprehensive research program to promote the translation of basic science investigation into clinical care. The center's co-directors, Ofer Reizes, PhD, Department of Cardiovascular & Metabolic Sciences and the Cancer Impact Area, Lerner Research Institute, and Peter Rose, MD, Department of Gynecologic Oncology, believe the CREGC is exceptionally positioned to change the landscape of gynecologic cancer research and care.

Through core resources and an infrastructure designed to promote collaboration and accelerate translational medicine, the CREGC supports research projects that explore possible causes of and treatments for a range of gynecologic cancers. These include:

- Characterizing genetic anomalies that confer radiation resistance in endometrial cancer.
- Identifying candidates for targeted immunotherapy to treat epithelial ovarian cancers.
- Developing therapies to overcome drug resistance in women with ovarian cancer who have *BRCA* mutations.
- Determining the role cancer stem cells and related molecules play in chemotherapy resistance.

In addition to the CREGC's efforts, Cleveland Clinic's Gynecologic Cancer Program offers patients the latest in gynecologic cancer management, including the newest drug therapies. "As part of NRG Oncology, an international cooperative research group funded by the National Cancer Institute and National Institutes of Health, we can offer patients who qualify access to investigational treatments through a wide range of clinical trials," states Dr. Rose. "Additional studies give eligible patients access to other new treatments under investigation in the CREGC, such as hyperthermic intraperitoneal chemotherapy (HIPEC)." The Gynecologic Oncology Cancer Program also offers minimally invasive surgery, sophisticated radiation therapy techniques and specialized imaging.

Reversing the traditional research paradigm

As a result of a $2 million gift from Robert J. and Laura J. Fogarty, Robert DeBernardo, MD, a gynecologic oncologist and Director of the Peritoneal Surface Malignancy Program, has been named the Laura J. Fogarty Endowed Chair in Women's Health for Uterine Cancer Research.

"The Fogartys recognize that there is a huge deficit in our knowledge of and ability to learn about these rare forms of cancer," says Dr. DeBernardo. "This generous endowment will help establish infrastructure to support our clinician-scientists to propel not only our understanding of the molecular mechanisms of these cancers, but ultimately to create a phase 1 clinical trial program where we can bring these discoveries to patients in need."

"Our goal is to reverse the traditional bench to bedside research paradigm," Dr. DeBernardo continues. "We will take tumor specimens directly from our patients and grow them in cell culture and in animal models. Then, we can apply innovative treatments and study the mechanisms through which these therapies are

working in ways not possible when treating patients with these cancers. In addition, government funding to study gynecologic cancers is shamefully inadequate; therefore, part of our mission will be to help raise awareness for these rare cancers."

This is the second endowed chair funded by the Fogartys at Cleveland Clinic. In 2016, the Fogarty family donated $1 million to create an endowed chair in Cleveland Clinic's Lerner Research Institute to support research into the causes and treatment of uterine cancer. Dr. Reizes, PhD is the Laura J. Fogarty Endowed Chair for Uterine Cancer Research.

"We are extremely grateful for this new gift and the generosity of the Fogarty family," says Beri Ridgeway, MD, Chair of the Ob/Gyn & Women's Health Institute. "This amazing gift will advance research and increase awareness for rare uterine cancers that would not be possible without this support."

BEST HOSPITALS U.S.News & World Report NATIONAL CANCER 2019-20

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Robert DeBernardo, MD


Cleveland Clinic
Nina Desai, PhD, HCLD

Advanced Imaging Techniques May Aid in Embryo Selection

Age-adjusted parameters for embryo development

Using data from continuous time-lapse (TL) monitoring of embryo culture, Cleveland Clinic researchers identified seven parameters associated with embryo chromosomal status and developed a predictive model that increases the probability of selecting chromosomally normal (euploid) blastocysts after in vitro fertilization (IVF).

Continuous embryo observation

Researchers analyzed morphokinetic data that had been prospectively collected from 2,493 zygotes subjected to aneuploidy screening at Cleveland Clinic between 2014 and 2017. During culture in the EmbryoScope® TL chamber, markers of development were determined by viewing captured videos. Blastocysts were scored according to maturity stage and inner cell mass/trophectoderm quality. Trophectoderm biopsy was performed on cells on either day five or six using a laser, and excised cells were sent for genetic analysis. Blastocysts found to be euploid were then transferred in the fresh cycle or subsequent frozen cycles.

"Overall, we found that only 37% of the blastocysts were chromosomally normal, which is what we expected since the majority of patients opting for preimplantation genetic screening (PGS) in our program are older," says Nina Desai, PhD, HCLD, Director of Cleveland Clinic's In Vitro Fertilization Lab. "PGS can help shorten the time to pregnancy by identifying chromosomally normal blastocysts, which is particularly important in our older patients whose reproductive potential rapidly declines with time. But PGS is a costly, labor-intensive and invasive technique. These limitations make alternative noninvasive methods, which potentially enhance the likelihood of selecting a euploid, attractive."

"We found that with every additional hour it took for an embryo to start to blastulate, the odds of it being chromosomally normal decreased by 4.5%, which is really significant," Dr. Desai continues. "We also looked at cutoff points and found that if an embryo started to blastulate in less than 96.2 hours, it was 1.5 times more likely to be chromosomally normal."

Dysmorphisms may be only momentarily visible

"One of the beauties of TL imaging is that you get a glimpse of events occurring at all hours — day or night. Often two embryos may look the same at a single time point, but when viewed continuously, they may differ radically. For instance, some two-cell embryos divide synchronously from two to four cells, whereas others may go to three cells and remain there for several hours, and further progression to four cells may take hours," says Dr. Desai. "Irregular divisions and other dysmorphisms may only be momentarily visible. We found an association between multinucleation in embryos and a lower rate of progressing through day four and becoming a blastocyst."

Dr. Desai and colleagues hope to apply the criteria from this research to embryo selection for transfer in patients who are not undergoing PGS to see if the parameters identified can, in fact, be used to incrementally improve pregnancy rates. "When we see patients whose embryos are growing more slowly, we always feel that is not a good sign, and this study provides us with data to support our suspicions," says Dr. Desai. "The age-adjusted parameters we identified appear to be independently associated with the likelihood of an embryo being chromosomally normal. Our results are dependent upon timing of embryonic development in a specific IVF laboratory. We hope that other clinics will develop their own models so that we can see whether there is significant overlap with our findings."

Efforts Underway to Improve Access to Comprehensive Healthcare for Women

Studies point to concerning trends in women's health

Many free-standing women's health clinics offer prenatal care, contraception and cancer screening exams. Recent studies point to concerning trends in women's health, including deaths from complications of pregnancy, rising sexually transmitted infection (STI) rates, trend-reversing increases in mortality from cervical cancer and limited access to effective emergency contraceptives, which may be related — at least in part — to clinic closures.

"As health professionals, any one of these issues should give us pause," states Beri Ridgeway, MD, Chair of the Ob/Gyn & Women's Health Institute. "Taken as a whole, however, we see reason to be concerned about the state of women's health in the United States."

Cervical cancer mortality rates reversing the gains made in the past several decades

A study presented at the 61st Annual Meeting of the American Society for Radiation Oncology found that states that experienced closures of women's health clinics saw a 2% decline in cervical cancer screenings compared to states without closures.[1] According to the study, which was not published by Cleveland Clinic researchers, nearly 100 comprehensive women's clinics closed between 2010 and 2013. The most significant screening declines were for women with no insurance, Hispanic women, women aged 21-34 years and unmarried women. Women who are socioeconomically disadvantaged or are non-Caucasian typically have the highest rates of morbidity and mortality from cervical cancer, making decreased access more concerning. This study found an increase in the risk of dying from cervical cancer among women in these communities.

"Cervical cancer is a disease of access," according to Miriam Cremer, MD, MPH, Director of Global Health Research for the Ob/Gyn & Women's Health Institute, and a member of the World Health Organization's Expert Group on Cervical Cancer Elimination. "In the United States, we haven't had a lot of cervical cancer because most people have access to screening and treatment. But when women don't have easy and affordable access to care, they may present with higher-grade lesions."

"Cervical cancer is definitely preventable," according to Dr. Cremer. "For this reason," she states, "we should absolutely be concerned about the loss of important health services for women who need them."

Reproductive health clinics offer many important preventive services, including the detection and treatment of sexually transmitted disease, cytology screening, and HPV testing and vaccination. The clinics also provide invaluable education and effective treatment for sexually transmitted diseases, which — if untreated — can have devastating effects on the health of populations.

According to a study published by the United Health Foundation, Ohio met only 14% of the need for publicly funded women's health services, ranking 48th among the states. "It is unacceptable that women are losing access to basic healthcare. Making sure these clinics stay open — and expand — will go a long way in keeping Ohio women healthy," Dr. Cremer says.

The political context of women's health

Political context also appears to play a role in access to effective birth control methods, including emergency contraceptives, according to a study co-authored by Pelin Batur, MD, a women's health specialist working in the Department of Subspecialty Women's Health within the Ob/Gyn & Women's Health Institute, and a member of multiple national committees involved in writing U.S. guideline

recommendations for contraceptive access and follow-up on abnormal cervical cancer screening.

Dr. Batur was part of a multi-institutional study of providers' knowledge of and attitudes toward emergency contraception. The group found that women in conservative-leaning counties may face difficulties obtaining emergency contraception from healthcare providers.

"Women in more politically conservative areas were much less likely to get emergency contraception services, which are part of the full spectrum of contraceptive services and can actually be the last chance to prevent pregnancy in a woman who is at high risk for complications, or who may be taking medications that can harm the fetus," Dr. Batur explains.

Ob/Gyns as educators and advocates

As evidenced by the advocacy work of Drs. Batur and Cremer, the Ob/Gyn & Women's Health Institute is committed to moving the needle on preventable mortality among women and children. Within Cleveland Clinic, Ob/Gyns play important roles, encouraging preventive services and adapting practice standards to current public health trends.

"For example," states Oluwatosin Goje, MD, an Ob/Gyn with fellowship training in reproductive infectious diseases, "we are expanding our prenatal STI screenings, and hope to provide education and guidance on how to treat STIs and prevent reinfection with expedited partner therapy."

Reference:

[1]Srivastava A, Barnes JM, Markovina S, Schwarz JK, Grigsby PW. The impact of the closure of women's health clinics on cervical cancer in the United States. *Int J Rad Oncol Biol Phys*. 2019:105(1);S98.

Congenital syphilis case leads to expanded prenatal STI screen to better serve our patients

Mystery rash leads to diagnosis

By Oluwatosin Goje, MD

A young woman, pregnant with her first child, had a negative result on the initial rapid plasma reagin (RPR) at 16 weeks. She delivered at term, the postpartum course was uneventful, and both mother and baby were discharged home on postoperative day three, with pediatric follow-up on day 11 of the baby's life.

The mother brought her 4-week-old baby to see the pediatrician for a rash on his arms and throat, which she had treated at home with bacitracin. The infant showed no other obvious symptoms at the time. Mother and newborn had a few more follow-up visits with the pediatrician to monitor the improvement and/or resolution of the rash, which was also noted in the diaper area. Because the mother had tested negative for syphilis prenatally, congenital syphilis was not considered as a contributing factor to the rash. Both the young mother and the pediatric team continued to seek answers. When the baby was 3 months old, a pediatric dermatologist was consulted about the persistent rash, and more laboratory testing, including RPR testing of the mother and newborn, was requested. This baby was diagnosed with congenital syphilis.

The baby was admitted and started on a 10-day course of intravenous penicillin. Additional studies indicated that the infant's organs, sight and hearing were unaffected. He had perianal condyloma lata, which fully resolved by 6 months of age, and a saddle nose deformity, and his cerebrospinal fluid screen was positive for syphilis with high titers. The infant was stable following antibiotic treatment.

Congenital syphilis despite standard prenatal care

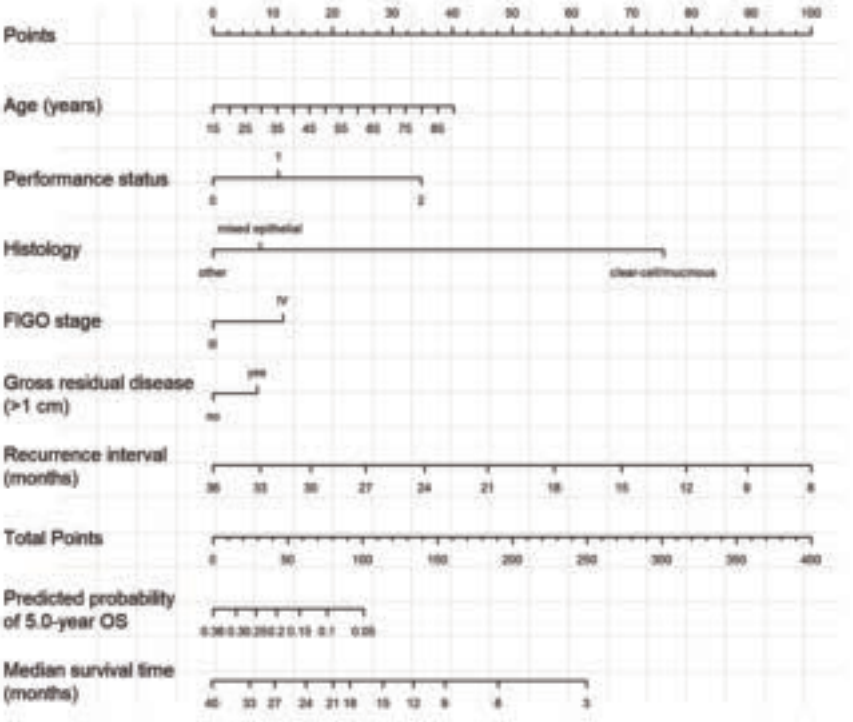
This is an unusual case with important teaching/learning points because the mother received high-quality, standard-of-care prenatal services and was negative for syphilis when tested early in her pregnancy. As part of the standard of care, all pregnant women receive the syphilis IgG screen or RPR test for syphilis at the first prenatal visit. The mother was infected during pregnancy, but after the RPR at 16 weeks' gestation. It is recommended that women considered at high risk for contracting syphilis during pregnancy be given a second syphilis test at 28-32 weeks of pregnancy.

Although Ohio comes in below the 2017 national average at 7.2 cases per 100,000 population, urban areas such as Franklin and Cuyahoga counties are high-incidence regions, with rates of 25.4 and 12.6 per 100,000, respectively.[1] For this reason, many women in our care meet the criteria for a second syphilis screen. Our hope is that, by recommending a universal second RPR/syphilis test at 28-32 weeks, maternal syphilis contracted during pregnancy would be appropriately diagnosed and treated with an antibiotic regimen at least 30 days prior to delivery.

Reference:

[1] Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2017. https://www.cdc.gov/std/stats17/tables/33.htm. Accessed on Nov. 12, 2019.

Tool to Help Predict Survival for Patients with Advanced-Stage Recurrent Ovarian Cancer



To use, find the patient's recurrence interval on the Recurrence axis, then draw a straight line upward to the Points axis to determine how many points toward death the patient receives for her recurrence interval. Do this again for the other axes, each time drawing a straight line upward toward the Points axis. Sum the points received for each predictor and find the sum on the Total Points axis. Draw a straight line down to the median survival time axis to find the patient's median survival time after recurrence of ovarian cancer.

Numerous past studies have shown that patients with ovarian cancer who respond to chemotherapy but then experience a recurrence within six months generally live another 10 months. Survival for patients with ovarian cancer who respond to chemotherapy but whose cancer recurs later, however, is more variable. The life expectancy for such patients is usually based on an average of how long all patients with recurrent ovarian cancer survive — 21 months.

Average survival times, however, do not provide much specific information for individual patients. Recently, a group of physicians from the NRG/Gynecologic Oncology Group analyzed clinical prognostic factors for survival after recurrence of high-grade, advanced-stage ovarian peritoneal tubal carcinoma. They then developed a nomogram to predict individual survival after recurrence.[1] "Patients want more specifics about their individual survival because it allows them to better plan for the future," says the study's first author, Peter Rose, MD, Section Head of Gynecologic Oncology.

The investigators identified a number of significant prognostic factors, including time to recurrence after initial chemotherapy, clear cell or mucinous histology, residual disease after primary surgery, performance status, stage IV disease, and age. These factors were utilized to develop a nomogram to predict estimated survival for each patient.

Recurrence time

Dr. Rose says the group's analysis shows that time to recurrence was by far the strongest variable for determining how long a patient would survive (accounting for 85% of the model). Residual disease, histology and performance status were the next most significant factors affecting survival after recurrence.

Reference:

[1] Rose PG, Java JJ, Salani R, et al. Nomogram for predicting individual survival after recurrence of advanced-stage, high-grade ovarian carcinoma. *Obstet Gynecol*. 2019;133(2):245-254.

Pelvic Exams Under Anesthesia Are Only for Clinical Indications, According to Cleveland Clinic Care Path

Care path emphasizes informed consent and learner participation on surgical team

Cleveland Clinic formalized its informed consent care path for pelvic exams that may be performed while a patient is under anesthesia for surgery. The purpose of the care path is to disseminate Cleveland Clinic's current best practices throughout the enterprise, as well as to educate future caregivers.

"We assembled a task force to formalize a care path regarding genital, pelvic and anorectal examinations under anesthesia. Our task force included a bioethicist as well as colleagues in colorectal surgery, general surgery, urology and gynecology," states Kenneth Edelman, MD, MBA, Cleveland Clinic Enterprise Medical Director for Patient Safety and Clinical Risk Management and Quality Improvement Officer in the Ob/Gyn & Women's Health Institute.

A national study conducted in 2010 found that while just over half of gynecologic surgery patients expect a medical student to be present during their procedures at an academic institution, only 19% were aware that a student might perform a pelvic examination on them while they were under anesthesia.[1] Among gynecologic surgery patients, 75% had had a pelvic examination under anesthesia performed by a medical student without prior discussion or approval, another national study indicates.[2,3]

"We take this issue very seriously," Dr. Edelman continues. "At Cleveland Clinic, the formalization of this care path demonstrates our collaborative efforts to support our patients' autonomy over their bodies while having procedures performed under anesthesia. Properly obtained informed consent not only explains the procedures to be performed, but also informs the patient that members of the surgical team — including medical students — may also perform an exam under anesthesia when medically necessary as part of the planned surgery. We do not perform procedures for the sole sake of education."

The Cleveland Clinic care path states that genital, pelvic and anorectal examinations under anesthesia should only be performed as medically indicated and in conjunction with the primary surgical procedure or for surgical planning, and not solely for educational purposes. All members of the Cleveland Clinic task force were provided with an electronic copy to distribute and discuss with their respective clinical departments on an ongoing basis. The care path was emailed to every clinical provider in the Ob/Gyn & Women's Health Institute, including the medical student clerkship director. This care path ensures that Cleveland Clinic's current best practices are followed throughout the health system, and may be a model for other systems.

References:

[1] Bibby J, Boyd N, Redman CWE, Luesley DM. Consent for vaginal examination by students on anaesthetised patients. *Lancet*. 1988:2(8620):1150.

[2] Wainberg S, Wrigley H, Fair J, Ross S. Teaching pelvic examinations under anesthesia: what do women think? *J Obstet* Gynaecol Can. 2010;32(1):49-53.

[3] Schniederjan S, Donovan GK. Ethics versus education: pelvic exams on anesthetized women. *J Okla State Med Assoc*. 2005;98(8):386-388.

Ob/Gyn & Women's Health Institute

At a Glance

13 centers across the region and in Florida

Chronic Pelvic Pain

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General Gynecology

Gynecologic Infectious Diseases

Gynecologic Oncology

Maternal-Fetal Medicine

Menstrual Disorders, Fibroids and Hysteroscopic Services

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Women's Weight Management

Shared medical appointments

The Ob/Gyn & Women's Health Institute offers shared medical appointments in these centers:

General Gynecology | Obstetrics and Family Medicine | General Obstetrics and Gynecology, Florida | Menstrual Disorders, Fibroids and Hysteroscopic Services | Specialized Women's Health | Urogynecology and Pelvic Floor Disorders | Women's Weight Management

Virtual visits

Virtual visits allow patients to communicate in real time (audio and video) with their providers from their home, office or elsewhere via a computer or smart-phone. The Ob/Gyn & Women's Health Institute offers virtual visits for its Metabolic Weight Management Program and for new, follow-up and postoperative visits in a variety of services.

Clinical research: by the numbers

$3.8 million in new research funding

205 studies

96 publications

Patient activity

Hospital admissions	10,698
Surgical procedures performed*	10,335
Deliveries	9,572
Outpatient visits	390,759
Shared medical appointments	1,296
Virtual visits	1,676

Caregivers

Ob/Gyns	154
Certified nurse midwives	24
Advanced practice nurses	42
Residents	24
Fellows	16

*Excludes cesarean sections

Statistics reported are from July 1, 2018, to June 30, 2019.

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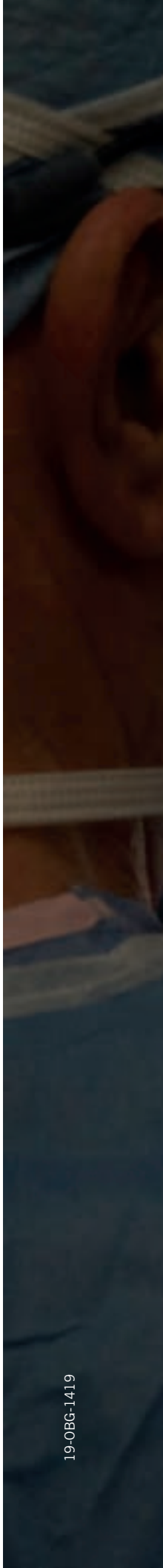

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