To Preserve Fertility in the Youngest Oncology Patients

JOHNS HOPKINS INVESTIGATORS are among the first in the world to examine ovarian tissue cryopreservation in young cancer patients needing gonadotoxic chemotherapy. Most children treated for cancer can now expect to be cured. However, in a significant majority, future fertility may be compromised by their disease or its treatment, says reproductive endocrinologist Mindy Christianson.

“While women have the option of freezing embryos or eggs, this is not an option in girls who have not reached puberty,” she says. “In young girls, there have been no viable fertility preservation options prior to ovarian tissue cryopreservation.”

In a pilot study that is a collaborative effort between Johns Hopkins’ Division of Pediatric General Surgery and its Department of Gynecology and Obstetrics, Christianson and pediatric surgeon and principal investigator Jeffrey Lukish are studying the viability of ovarian tissue cryopreservation in six young cancer patients. The idea is to enable long-term storage of significant numbers of primordial follicles.

“We believe that this pilot study will open the field of ovarian cryopreservation in children,” says Lukish. “By providing an evidence base for future practice, the potential benefit to the young girl with cancer is significant.”

They are collecting ovarian tissue at the time patients’ central venous catheters are placed. Part of the sample is cryopreserved for the patient for future use; additional samples are cryopreserved and then transplanted into severe combined immunodeficiency mice to assess the effectiveness of ovarian tissue cryopreservation in this population.

“It’s a very new technology and still considered experimental,” Lukish says. Only 30 babies have been born worldwide from cryopreserved tissue. “We’re hoping in 15 to 20 years, when these girls reach maturity, that technology will have evolved to where we will have better ways to retrieve eggs from the tissue.”

The Johns Hopkins Fertility Center is one of about 100 centers in the world that freeze ovarian tissue under an Institutional Review Board-approved protocol. The fertility center’s lab director, Yulian Zhao, has been pivotal in bringing this technology to Johns Hopkins and plans to add cryopreservation options.

Fertility preservation is a growing concern among patients and their parents, Christianson says. Between 2002 and 2012, the Johns Hopkins Fertility Center counseled 368 females about fertility preservation, a quarter of whom were 18 or younger. Some patients don’t pursue it because of poor prognosis or cost. Participation in the study covers the tissue collection and storage for three years. The investigators so far have enrolled four girls. Although the study is still in the early stages, Christianson says the frozen tissue has shown good viability, and she hopes to expand the research.

The study is funded by the Robert Garrett Fund for the Surgical Treatment of Children as well as a Fertility Preservation Options Research Fellowship Grant from the American College of Obstetricians and Gynecologists and Ferring Pharmaceuticals.

To refer a patient for fertility preservation, call the Johns Hopkins Fertility Center at 443-997-0400. To refer a patient for the ovarian cryopreservation study, call 410-955-5628.

Mindy Christianson and Jeffrey Lukish are studying whether eggs can eventually be retrieved from frozen ovarian tissue harvested from young girls before they undergo cancer treatment.
Dear Colleague,

As the newly appointed director of the Department of Gynecology and Obstetrics, I am truly privileged to work with such a talented team. I’m especially proud of the surgical boundaries we are pushing and the groundbreaking research discoveries we are making in a field that is changing rapidly.

The vision for our department involves a significant investment in cutting-edge clinical programs and expanding our specialized faculty to continue to be at the forefront of advances in the field.

The articles in this issue of Innovations in Gynecology demonstrate the range of our expertise and illustrate our commitment to advancing care for women of all ages: using amnioinfusion to treat a developing fetus with bilateral renal agenesis, combining novel therapies to treat pelvic pain, ovarian tissue cryopreservation in young cancer patients, using 3-D ultrasound to explain certain pelvic floor disorders, reducing incision sizes for both benign and oncology procedures.

We hope you enjoy this brief snapshot of our department’s innovations. Please call on us to learn how we can contribute to your practice.

Andy Satin, M.D.
Director
Johns Hopkins Department of Gynecology and Obstetrics

For urgent referrals and consultations: 1-800-765-5447 (Hopkins Access Line)

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Doing More with LESS

F gynecologic oncology surgeon Amanda Nickles Fader had her way, most gynecologic procedures would be performed through tiny incision. She’s working hard to make that happen.

Studies from the past 15 years have shown that minimally invasive surgical (MIS) approaches to treating gynecologic conditions are superior to surgery performed through large incisions, says Fader, who joined Johns Hopkins in April as director of the Kelly Gynecologic Oncology Service and the Minimally Invasive Surgery Center in the Department of Gynecology and Obstetrics. “The recovery is faster,” she says, “there are fewer perioperative complications and less pain, hospitalizations are shorter, and women get back to their lives more quickly.”

Fader is now heading an evolving center of excellence in minimally invasive gynecologic surgery and surgical innovation at Johns Hopkins, one of few hospitals nationwide offering the gamut of minimally invasive procedures for benign or cancerous gynecologic problems. The techniques include laparoscopic single-site surgery (LESS), microlaparoscopy and robotic surgery. With conventional laparoscopic or robotic surgeries, the procedures are performed through three to five abdominal incisions. But studies suggest that complications like risk of infection, hernia, visceral injury, nerve entrapment and persistent incisional pain can still occur. During LESS procedures, surgeons operate through one dime-size incision in the navel, where there are few nerves, muscle or blood vessels. Patients can’t see the incision once it’s healed and they require very little pain medication after surgery.

With microlaparoscopy, tiny 2-3 mm incisions are made and miniature laparoscopic instruments are used. “Going from 5-12 mm incisions to 2-3 mm incisions may seem like a small difference,” Fader says, “but it’s the difference between having to repair an incision with a potentially painful stitch to avoid a hernia compared with using a little skin glue or a Band-Aid.”

Early outcomes show that in the hands of experienced surgeons, these techniques can be used safely even for very difficult operations, says Fader, including the removal of ovarian cysts and masses; uterine fibroids; hysterectomies; and select uterine, cervical and ovarian cancer-staging procedures.

Fader and colleagues Stacey Scheib, Edward Tanner and Kara Long Roche are also conducting clinical trials using robotic surgical techniques to detect sentinel lymph nodes in gynecologic cancer patients. Blue or green dyes are injected into the cervix to identify the first group of draining lymph nodes most likely to be involved in uterine or cervical cancer if it has spread, allowing the surgeons to remove fewer lymph nodes. This decreases the risk of complications for patients. Fader and colleagues are also studying the merger of robotics and single-site technology—an option approved by the FDA in February—that may allow for surgery performed through the navel to be performed more easily.

At Johns Hopkins, 85 percent of endometrial and cervical cancer-staging procedures, nearly 100 percent of risk-reducing uterine and ovarian procedures, and 75 percent of overall hysterectomies are performed minimally invasively. Fader alone performs approximately 300 of these procedures annually.

“Our philosophy,” says Amanda Nickles Fader, “is to offer patients the most state-of-the-art treatments that result in outstanding outcomes and don’t completely disrupt their quality of life.”
Studying the Causes of Pelvic Floor Problems

WHY DO SOME WOMEN DEVELOP pelvic floor disorders years after giving birth while others don’t? The answer could lie in muscles deep in the vagina.

In a long-term study, urogynecologist Victoria Handa has been following a group of 1,500 women who gave birth five to 15 years ago to better understand the cause of pelvic floor disorders and come up with better treatments. What’s become apparent is that the pelvic floor’s levator ani muscles play a huge role in injuries sustained during childbirth, Handa says.

Her research so far has found that women with a history of forceps-assisted vaginal delivery are twice as likely to have prolapse compared to women without that history; by contrast, vacuum delivery did not appear to increase the risk of pelvic floor disorders. A possible explanation, she says, is the prevalence of pelvic floor muscle trauma between the delivery types.

More recently, in a smaller study funded by the American Congress of Obstetricians and Gynecologists, Handa and gyn/ob fellow Hafsa Memon looked at birth history among 89 women from their larger study population, comparing women who had undergone at least one forceps delivery to women who had undergone at least one vacuum birth. Using three-dimensional ultrasound to identify obstetrical injury to the pelvic muscles, they found that the odds of levator ani muscle avulsion were increased dramatically in the forceps group. Women with a history of forceps delivery also had other evidence of structural and functional changes in the pelvic muscles. The results, being submitted for publication, suggest that muscle injuries are especially common after forceps birth, says Handa.

Pelvic floor disorders like bladder incontinence and pelvic organ prolapse affect up to one in six women with a history of vaginal birth, and operations to repair these problems are as common as breast cancer, says Handa. Yet people don’t talk about it because it’s personal, and maybe embarrassing,” she says.

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Where Pelvic Pain Meets Its Match

Gynecologist Stacey Scheib points to a recent patient case as an example of how multidisciplinary care can best help women with pelvic pain.

By the time the woman came to see Scheib, she was in so much pain that she could barely sit down in a chair. On initial exam, her pelvic floor was so much in spasm and tender that Scheib was unable to fully assess her pelvis. So Scheib coordinated a series of steps with Johns Hopkins experts to help her.

She first ordered compounded medication from Johns Hopkins’ pharmacy to help relax the pelvic floor muscles, then sent the patient for pelvic physical therapy. Scheib also collaborated with Johns Hopkins interventional radiologist Kelvin Hong, who injected botulinum A toxin directly to the patient’s pelvic muscles to help with pain relief.

Scheib then was able to perform a more extensive assessment of the patient’s pelvis and obtain an MRI scan, which revealed a tender cervix scarred to the surrounding tissues and a right-sided pelvic mass. Finally, Scheib performed a robotic-assisted laparoscopic trachelectomy, extensive lysis of adhesions and excision of a solid retroperitoneal endometriosis mass. Today, the patient is nearly pain-free.

“Any one intervention would not have resolved her pain, but together they have provided the relief the patient was seeking,” says Scheib. “She can now sit in a car comfortably, ride her bicycle and play strengthening exercises like Kegels or more extensive physical therapy for patients to reverse pelvic floor problems or prevent them from worsening, and which patients will have recurring problems. “These are the things ultrasound has a lot of promise to help us understand,” Handa says.

For more information or to refer a patient, call 443-997-0400.
Thanks to perinatologist Jessica Bienstock, a Washington state congresswoman is now a happy mother. Rep. Jaime Herrera Beutler was referred to Johns Hopkins this spring for a third opinion after her fetus was diagnosed with bilateral renal agenesis. To confirm the diagnosis by ultrasound, Bienstock needed to put fluid into the amniotic sac by carefully infusing saline solution into the uterus. She saw what previous physicians had noted: a fetus without kidneys, and a deformed chest and head. But when Beutler returned a week later, a new ultrasound revealed some fluid had remained. Not only were the fetus’ head and chest developing more normally, the baby was actively moving around.

“We were thrilled,” says Bienstock. “Things were looking better, and the baby was trying to practice breathing.”

Beutler asked for an additional infusion and after discussing the risks with Bienstock, agreed to go ahead. Beutler received five infusions over several weeks before going into labor in July. Her daughter was born 12 weeks premature at an Oregon hospital and has been undergoing dialysis at Stanford’s Lucille Packard Children’s Hospital.

“This case is unprecedented,” says Bienstock. “It would be premature to say bilateral renal agenesis should always be treated using serial amnioinfusion, but this suggests it can be part of the conversation.”

Bienstock, who is planning a formal study of amnioinfusion, has now counseled several other patients referred from around the country.

“Not every patient with absent amniotic fluid is a candidate for amnioinfusion,” she cautions. “It’s only an appropriate treatment for fetuses with no kidneys, or for those with non-functioning kidneys, who don’t have other genetic or serious anomalies. We are not currently looking at this treatment for low fluid of other etiologies.”

Treatments also can be disruptive for patients and their families, who are encouraged to relocate to the Baltimore area for up to two years. Patients undergo ultrasounds and saline infusions once or twice a week, and babies born must undergo regular peritoneal dialysis treatments.

For more information or to refer a patient, call 443-997-0400.