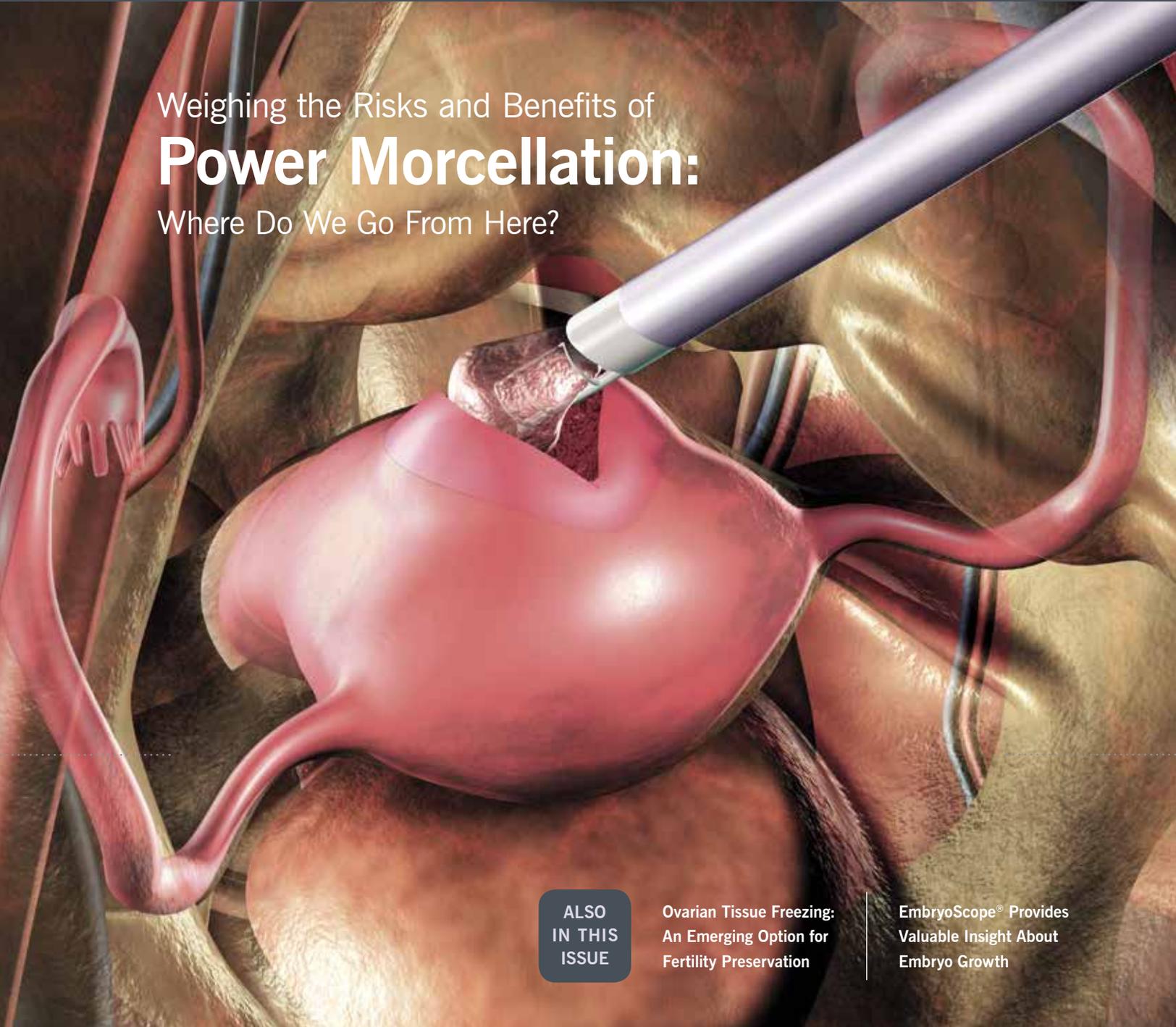


Ob/Gyn & Women's Health Perspectives

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



Weighing the Risks and Benefits of
Power Morcellation:
Where Do We Go From Here?

ALSO
IN THIS
ISSUE

Ovarian Tissue Freezing:
An Emerging Option for
Fertility Preservation

EmbryoScope® Provides
Valuable Insight About
Embryo Growth



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The Cleveland Clinic Way By Toby Cosgrove, MD, CEO and President of Cleveland Clinic

Great things happen when a medical center puts patients first. For details or to order a copy of this new book, visit clevelandclinic.org/ClevelandClinicWay.

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Dear Colleagues and Friends:

As our patients face complex obstetric and gynecologic problems, they deserve the most innovative care we can provide. But with innovation comes the responsibility to constantly, rigorously evaluate the effectiveness of what we're doing, and to respond to challenges as they arise.



You'll find examples of both of those imperatives — to innovate and to perform clear-eyed reassessment — in this latest issue of *Ob/Gyn & Women's Health Perspectives*.

In our cover story, Marie Fidela Paraiso, MD, who heads Cleveland Clinic Ob/Gyn & Women's Health Institute's Urogynecology and Reconstructive Pelvic Surgery Section, offers practical advice about how to proceed in the wake of the Food and Drug Administration's safety communications in 2014 regarding laparoscopic power morcellation's potential to spread undiagnosed cancerous tissue beyond the uterus in hysterectomy or myomectomy.

Dr. Paraiso served on both the American Association of Gynecologic Laparoscopists and American Congress of Obstetricians and Gynecologists panels that issued power morcellation recommendations, so she is well-positioned to offer guidance as we determine the appropriate path forward.

Also in this issue, Rebecca Flyckt, MD, the Director of our Fertility Preservation and Cancer Program, gives an informative overview of ovarian tissue cryopreservation, a novel emerging technique that helps girls and women facing gonadotoxic chemotherapy preserve the option to bear a child in the future. And Nina Desai, PhD, HCLD, who directs our In Vitro Fertilization Laboratory, provides an update on our early clinical experience and outcomes with EmbryoScope®, an exciting new time-lapse imaging system that monitors embryogenesis in IVF and is aiding selection of the best embryos for uterine transfer.

These articles reflect Cleveland Clinic's mission to develop and share the best in new knowledge and technology, and to constantly advance the care we provide our patients. In 2014, *U.S. News & World Report* once again ranked our gynecology program the nation's third-best. We're honored by, and appreciative of, this recognition from our peers. It's a reminder that we must constantly strive to improve. Please follow our progress in these pages; in our annual Outcomes book, available online at clevelandclinic.org/outcomes; and on Cleveland Clinic's new blog for physicians and healthcare professionals, Consult QD, at consultqd.clevelandclinic.org.

I look forward to continued collaborations with you, and welcome your questions and feedback.

Sincerely,

Tommaso Falcone, MD

Professor & Chairman, Department of Obstetrics and Gynecology
Chairman, Ob/Gyn & Women's Health Institute

Weighing the Risks and Benefits of Power Morcellation: Where Do We Go From Here?

Ob/Gyn groups voice support of technique to FDA

By Marie Fidela Paraiso, MD

It is clear that minimally invasive gynecologic surgery (MIGS) has significantly improved the treatment of benign conditions and malignancies.

In the last two decades, power morcellation has become one of the most important items in our surgical toolkit for minimally invasive hysterectomy and myomectomy in patients with benign conditions.

However, in April the Food and Drug Administration (FDA) issued a safety communication discouraging the use of the technique in these cases due to the risk of exposing the peritoneal cavity to cancerous tissue from an undetected uterine malignancy. The FDA estimates that 1 in 352 women undergoing hysterectomy or myomectomy for fibroids has undetected uterine sarcoma. Subsequently, Johnson & Johnson, one of the largest manufacturers of power morcellators, suspended sales and distribution of the devices.

The FDA formed an advisory committee to examine the morcellation issue. In late November the agency took additional steps. Although it did not ban power morcellation, the agency warned against its use in most hysterectomies and myomectomies for uterine fibroids. The FDA recommended a warning label on power morcellators that includes two contraindications (in patients who are peri- or postmenopausal or are candidates for en bloc tissue removal, and in cases where tissue to be morcellated is known or suspected to contain malignancy). The agency will consider other risk reduction steps.

Cleveland Clinic and many other health systems suspended the use of power morcellation while awaiting the FDA's final determination.

Meanwhile, clinical discussions have continued. After analyzing the risk-benefit ratio of power morcellation for benign conditions, some clinical experts and ob/gyn medical societies have stated that insufficient evidence exists to discontinue the technique in low-risk, appropriately screened patients, and that the risk of spreading an occult malignancy may not be as high as the FDA's estimate.

The FDA's power morcellation advisory committee has received input from major ob/gyn associations such as the American Association of Gynecologic Laparoscopists (AAGL), American Congress of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO). As one of only two surgeons to serve on the AAGL and ACOG panels that issued recommendations about power morcellation, and based on my clinical experience, I believe the following points are important:

- **The vast majority of hysterectomies and myomectomies performed in the United States are for benign fibroids. Power morcellation clearly should not be used in treating known or suspected malignancy.** MIGS using laparoscopic or robotic techniques — often with intracorporeal morcellation — short-

ens surgery times, expands surgical approach options and decreases complications. For benign conditions, the advantages of MIGS versus laparotomy are well-supported. There are some surgical alternatives to intracorporeal morcellation, such as removing the uterus through a mini-laparotomy or enlarged port-site incision; morcellating the specimen vaginally; morcellating the uterus inside a specimen bag intracorporeally; or using cold-knife tissue extraction once the uterus is placed in a bag. However, specimen bags have limitations (i.e., few options in the case of an enlarged uterus, the lack of bags designed for power morcellation, and lack of data verifying the bags' safety and effectiveness).

- **MIGS patients should be carefully selected based on age and risk factors.** In our practice, we consider patients younger than 35 who have had an appropriate preoperative evaluation to be at very low risk for an occult malignancy. We also evaluate and consider other sarcoma risk factors such as inheritable diseases or previous radiation.
- **Candidates for MIGS who might require power morcellation should be evaluated preoperatively for the possibility of uterine or cervical malignancy.** In our practice, we perform an endometrial biopsy if appropriate. Additionally, the cervical screening must be negative. If we are concerned about a rapidly

enlarging uterus, we perform additional diagnostic tests. While certain malignancies such as leiomyosarcomas can be difficult to detect preoperatively, appropriate screening can detect 38 to 68 percent of cases. An investigation cited by the AAGL found that the combined mortality from leiomyosarcoma and the potential dissemination through power morcellation would still be less than the mortality from open hysterectomy.

- **The FDA may have overstated the risk of occult malignancy.** The ob/gyn societies criticized the data the FDA used to arrive at the 1 in 352 risk for undetected malignancy. Existing data are limited, and most studies the FDA cited were retrospective and of poor quality. In documents submitted to the FDA, Pritts et al. cited studies that put the actual risk anywhere from 1 in 360 to 1 in 8,333. In addition, no large-scale studies have been published that specifically evaluate the risk of occult malignancy in the population most likely to have MIGS with intracorporeal morcellation — premenopausal women with benign-appearing symptomatic fibroids who have been carefully screened.
- **Informed consent is essential.** At Cleveland Clinic, we are updating our informed consent documents to clearly outline the risks and benefits not only of MIGS with power morcellation, but also of the alternatives. The informed consent will be part of a care path — standardized, actionable guidelines — that we are developing to address surgical options in this realm. If/when we resume power morcellation, we plan to create a prospective database to track outcomes.

At Cleveland Clinic, we have created a committee that includes gynecologic oncologists and minimally invasive surgeons, with input from pathologists and



Marie Fidela Paraiso, MD

radiologists, so that we can make the best recommendations for our patients. We also plan to develop a risk factor model.

It is truly unfortunate that a few women with undiagnosed cancers have had peritoneal cavity exposure during MIGS with power morcellation. However, in measuring the risk/benefit ratio, converting all power morcellation procedures to open surgery would likely increase morbidity and mortality and harm more patients. More research, education and improved tissue extraction techniques could enhance the safety of power morcellation. With meticulous adherence to preoperative patient selection guidelines and informed consent, the AAGL believes appropriately performed power morcellation outweighs the risk of laparotomy in low-risk patients and is an option that patients and their gynecologists should carefully consider. ■

Dr. Paraiso is the Section Head of Urogynecology and Reconstructive Pelvic Surgery in Cleveland Clinic's Ob/Gyn & Women's Health Institute and a Professor of Surgery at Cleveland Clinic Lerner College of Medicine. She can be reached at 216.444.3428 or paraism@ccf.org.

Additional Reading

ACOG Special Report on Power Morcellation and Occult Malignancy in Gynecologic Surgery. Available at: <http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Power-Morcellation-and-Occult-Malignancy-in-Gynecologic-Surgery>

AAGL Statement to the FDA on Power Morcellation. Available at: <http://www.aagl.org/aaglnews/member-update-5-aagl-response-to-fda-guidance-on-use-of-power-morcellation-during-tissue-extraction-for-uterine-fibroids/>

Statement of the SGO to the FDA's Obstetrics and Gynecology Medical Devices Advisory Committee Concerning Safety of Laparoscopic Power Morcellation. Available at: <https://www.sgo.org/wp-content/uploads/2014/04/SGO-Testimony-to-FDA-on-Power-Morcellation-FINAL.pdf>

Tissue extraction during minimally invasive gynecology: Counseling the patient [*OBG Manag.* 2014;26(10):41,42,44,56]. Available at: http://www.obgmanagement.com/index.php?id=31595&type=98&tx_ttnews%5Btt_news%5D=301185&cHash=da03e20e36

EmbryoScope Provides Valuable Insight About Embryo Growth

Time-lapse Imaging Aids Selection of Best Embryos for Uterine Transfer

By Nina Desai, PhD, HCLD

In vitro fertilization (IVF) success rates have increased since the birth of the first IVF baby in 1978. However, in 2012 the implantation rate per embryo transferred in patients younger than 35 was still only 37.5 percent, according to the Society for Assisted Reproductive Technologies national IVF registry.

To maximize the chance of pregnancy, centers typically transfer two to three embryos per cycle, despite the increased risk of multiple pregnancy and its associated neonatal and maternal complications. The most critical step during IVF is embryo selection for transfer.

For the last two decades, this selection has been based solely on morphology. Currently, these morphological assessments are limited to once a day, since repeated removal of the embryo culture dish from the incubator environment may result in exposure of embryos to undesired temperature and pH shifts. Often, embryo morphology is very similar, making selection difficult (Figure 1). Improvements in embryo selection for transfer could help reduce overall multiple pregnancy rates after IVF by allowing the transfer of fewer embryos without compromising the patient's opportunity to achieve a pregnancy.

Imaging Reveals Dynamics of Embryonic Growth

The introduction of time-lapse imaging systems to clinical IVF laboratories has enabled more detailed observations on embryo developmental kinetics. It has become clear that embryo development is a dynamic event, and static observations of embryonic growth can be limiting in their ability to discern differences among embryos at similar cell stages.

Numerous data suggest that the precise timing of specific events such as pronu-

clear formation, syngamy, cell division, cell cycle intervals, synchronicity of cell division and initiation of blastocyst formation are indicators of an embryo's developmental potential. The ability to continuously monitor an embryo's progression toward these benchmarks may therefore aid selection of the best embryos for uterine transfer.

In 2012 Cleveland Clinic's IVF laboratory acquired its first time-lapse imaging system, the EmbryoScope® (Unisense Fertilitech, Denmark). This elegantly engineered instrument is an incubator with a built-in microscope and high-definition camera, allowing continuous monitoring of embryo growth. The chamber design and camera software allow imaging of as many as 72 embryos (six patient slides with 12 embryos apiece) in five focal planes every 15 minutes.

After years of "quick peeks" at embryos once daily, being able to actually visualize the journey from fertilization through blastocyst formation to hatching has been amazing. Very quickly we began to see early cleavage and nuclear anomalies not previously evident, and to understand the impact of these, as well as the timing of cell cycle events, on subsequent pregnancy outcomes.

Study Provides Initial Outcomes Data

Our first paper on EmbryoScope use and time-lapse imaging was recently published in *Reproductive Biology and Endocrinology*. This study presents our

first experiences and initial clinical outcomes data with continuous time-lapse imaging in the EmbryoScope. We analyzed morphokinetic data collected every 15 minutes from 648 embryos cultured in vitro for five days. Timing of early cell division of the zygote to two, four and eight cells as well as progression to morula and blastocyst stages were important. Cell cycle intervals and time to complete synchronous divisions also provided insight into the embryo's potential.

The controlled culture environment that the EmbryoScope provided, allowing undisturbed growth with continuous imaging, positively impacted clinical results. Our clinical outcome data are shown in Table 1. The clinical pregnancy rate for day 5 transfers was 72 percent (41/57). The implantation rate per embryo transferred was 50 percent (61/121). This study allowed us to define the optimal timing for transition from a one-cell zygote to the blastocyst stage.

The first three cleavage events — transforming from one to two cells, two to four cells and four to eight cells — were especially telling. For instance, a two-cell embryo that started to divide but then rested at the three-cell stage for several hours had less potential than an embryo in which both cells divided more synchronously (within an hour), forming a four-cell embryo. Time-lapse imaging allowed us to precisely monitor cell cycle length, time for each blastomere to complete its division, and the resting phase of the embryo.

Also interesting were some of the cleavage anomalies that we witnessed for the first time. These included division of a single cell into three blastomeres, reverse cleavage where a blastomere was reabsorbed, and the presence of multiple nuclei within a single cell. Deselection of embryos with these traits is now routinely performed in our laboratory.

From our initial work we concluded that early morphokinetic parameters differ between embryos that make good-quality blastocysts and those that fail to blastulate or that show poor blastocyst morphology. Even among good-quality transferred blastocysts, we were able to detect differences between implanting and nonimplanting blastocysts using time-lapse data. This latter observation may be especially valuable as our laboratory moves toward elective single-embryo transfer.

An Asset for Patient Counseling and Data Sharing

The EmbryoScope and future generations of time-lapse systems will revolutionize the laboratory practice of embryology. Such systems allow hands-free monitoring of embryo growth and development of computer algorithms for enhanced embryo selection. The remote access capability of such systems means information can be easily shared with the fertility team.

For physicians, time-lapse videos may prove an invaluable tool in counseling patients and helping them understand IVF failures. This leading-edge technology has already become integral to IVF at Cleveland Clinic, leading to increasing pregnancy and implantation rates. ■

Dr. Desai is a staff member of Cleveland Clinic's Department of Obstetrics and Gynecology and Director of the IVF laboratory. She can be reached at desain@ccf.org or 216.839.2907.

Table 1. Clinical outcomes data after culture and time-lapse imaging (TL) in EmbryoScope.

Patients	60
Transfers	57 ^a
Mean age (years)	33.5 ± 4.0
Total TL embryos examined	678
Embryos cultured	11.0 ± 2.8
Blastocyst formation	71%
Embryos transferred	1.9 ± 0.8
Positive pregnancy test	81% (46/57)
Clinical pregnancy per transfer ^b	72% (41/57)
Implantation rate ^c	50% (61/121)
Live birth rate	68% (39/57)
Singleton deliveries	54%
Twin deliveries	49%

- a Three cycles with no transfer due to hyperstimulation/all blastocysts frozen
- b Clinical pregnancy confirmed by presence of fetal cardiac activity
- c Implantation rate = total fetal hearts/total embryos transferred

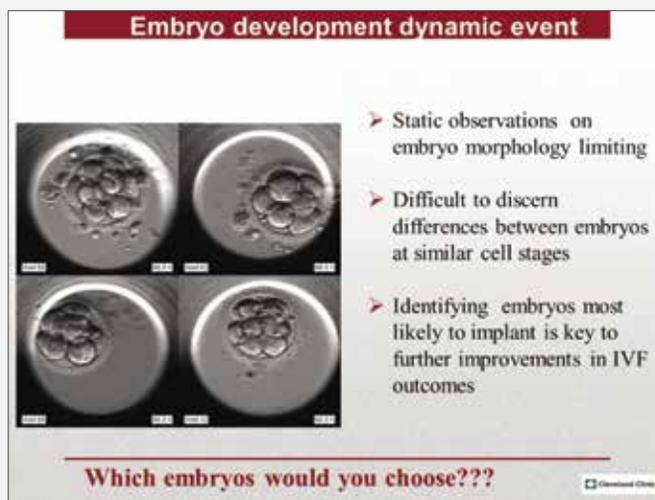


Figure 1. Micrograph depicts four embryos on day 3 of culture. With conventional culture, the embryologist typically selects two embryos for transfer based strictly on morphology. Only two of the four embryos shown will develop to blastocysts with the ability to implant (wells 2, 9) while the remaining two will arrest in culture. Time-lapse imaging offers additional data on the timing of early cleavages, synchronicity of cell divisions, and the presence of cleavage or nuclear anomalies, which could aid in distinguishing among embryos of similar morphology and ultimately in selecting embryos with the greatest implantation potential.

Ovarian Tissue Freezing: An Emerging Option for Fertility Preservation

Experimental Technique Available for Children and Adults

By Rebecca Flyckt, MD

Many women diagnosed with cancer in the United States are of reproductive age. As treatments become increasingly effective, more women are surviving their cancers and subsequently pursuing childbearing. Unfortunately, the agents involved in effective cancer treatment are also often damaging to the ovaries, and their use can result in menstrual dysfunction, infertility or premature menopause.

Until recently, women undergoing gonadotoxic chemotherapy had few options for fertility preservation. The gold standard, egg and embryo freezing, cannot be used for prepubertal girls and is not an option for adult women who must pursue immediate treatment for their cancers. Ovarian stimulation for egg and embryo freezing requires a delay of several weeks and involves heightened hormone levels, which are not advised for certain kinds of tumors.

A Source of Many Viable Oocytes

In the last few decades, ovarian tissue freezing has emerged as a promising approach to fertility preservation. Instead of a small number of eggs or embryos, frozen ovarian tissue may contain thousands of viable oocytes.

The American Society of Reproductive Medicine still considers ovarian tissue cryopreservation to be experimental in humans, and it can only be performed under an Institutional Review Board-approved protocol with detailed informed consent. At least 26 live births have been recorded worldwide using this technique. Cleveland Clinic now offers ovarian tissue freezing for pediatric and adult populations.

In this procedure, ovarian cortical tissue is harvested (often using minimally invasive techniques) and frozen. The blood supply to the medulla of the ovary (which is left in situ) is carefully preserved.

No Chemotherapy Delays or Need for Immunosuppression

This procedure can be performed as a same-day surgery with rapid recovery and no delay in chemotherapy. It can also be easily performed on children and/or combined with other procedures under anesthesia (such as Mediport placement). Children require special ethical consideration and informed consent can be obtained from both the parent and the child (when appropriate).

Once the patient has recovered from cancer treatment and is ready to pursue fertility, the ovarian tissue can be transplanted back into the individual, either in the location of the ovary (orthotopic transplantation) or in alternative locations (heterotopic transplantation). Fine sutures secure the strips of ovary, which can then develop a healthy blood supply in several locations.

Transplantation typically results in resumption of normal endocrine and reproductive function within several months. Opportunities exist for assisted reproduction or spontaneous pregnancy. Unlike other grafts, because ovarian tissue transplantation involves the original host, no special medications or immunosuppressants are needed.

As in vitro maturation (IVM) of immature oocytes becomes more viable in the embryology lab, it is possible that thawed ovarian tissue could be used for IVM without requiring reimplantation at all. Indeed, the risk of malignant

contamination of the ovarian tissue is a concern with this type of transplant (especially with hematologic malignancies); research is ongoing to determine the best method for salvaging viable oocytes from affected ovarian tissue.

Applications Beyond Cancer Patients

Although this technique was developed for patients with malignancies, it has wider applications. In addition to being the only option for children, it is appropriate for patients with autoimmune disorders (e.g., lupus erythematosus) or hematologic disorders that require chemotherapy or stem cell transplant. Patients undergoing risk-reducing oophorectomy for BRCA carrier status may also desire to freeze ovarian tissue. Finally, ovarian tissue freezing is available electively for healthy women who wish to delay childbearing, with the understanding that this technology is experimental.

Ovarian tissue freezing preserves fertility in patients who might not otherwise have options. It offers adult women an alternative to ovarian stimulation. We are pleased to provide this service for those who need it. ■

Dr. Flyckt is an associate staff member of Cleveland Clinic's Department of Obstetrics and Gynecology and Director of the Fertility Preservation and Cancer Program. She can be reached at flycktr@ccf.org or 216.838.3150.

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In 2014, Cleveland Clinic was ranked one of America's top four hospitals in *U.S. News & World Report's* "Best Hospitals" survey. The survey ranks Cleveland Clinic among the nation's top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 20th consecutive year) and urologic care.

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