Options for Preserving Fertility
Dear Colleagues:

I am delighted to bring you this issue of Ob/Gyn & Women’s Health Perspectives, which is designed to provide insight on and context for the many initiatives underway at Cleveland Clinic. In this issue, we focus on maternity and cancer.

First, we provide an update on some of our pioneering work in fertility. We detail the various fertility options available to women and specifically to patients with and survivors of cancer and other debilitating diseases requiring aggressive therapies.

We also talk about the challenges associated both with diagnosis and treatment of cancer during pregnancy and answer the most often asked questions from expectant moms and dads — and their doctors — relating to this topic.

Our experts discuss some fascinating research and present a case study of a patient with an aggressive cancer who met the criteria for an experimental treatment, absent a definitive standard of care.

Finally, we look at the rising maternal mortality rate in the United States and discuss this disturbing trend’s causes and implications. Why are more women in this country dying from pregnancy complications than women in any other industrialized nation? There are a host of reasons, data and potential solutions to consider. We do believe our multidisciplinary approach to pregnancy — from fertility through birth and beyond — is proving effective in ensuring excellent care for mothers and their families, even in the most challenging of circumstances.

Steadfast in our commitment to advancing women’s health, we continue to invest in lifesaving research, patient-centered care and critical education to deliver both immediate and long-term results.

Please know your questions and feedback are always welcome.

Sincerely,

Beri Ridgeway, MD
Acting Chair, Department of Obstetrics and Gynecology
Acting Chair, Ob/Gyn & Women’s Health Institute
216.444.6601 | ridgewb@ccf.org

Stay Connected with Cleveland Clinic’s Ob/Gyn & Women’s Health Institute

Consult QD — Ob/Gyn & Women’s Health
News, research and perspectives from Cleveland Clinic experts:
consultqd.clevelandclinic.org/obgyn

Facebook.com/CMEClevelandClinic

@CleClinicMD

clevelandclinic.org/MDlinkedin

clevelandclinic.org/obgyn

Subscribe to Ob/Gyn Perspectives to learn about the latest innovations, research and educational programs from Cleveland Clinic.
clevelandclinic.org/obgynnews

About Cleveland Clinic

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

In 2018, Cleveland Clinic ranked No. 2 in U.S. News & World Report’s “Best Hospitals” survey. The survey ranks Cleveland Clinic among the nation’s top 10 hospitals in 13 specialty areas, and the top hospital in heart care (for the 24th consecutive year) and urologic care.

Managing Editor: Ann Bakuniene-Milanowski
Art Director: Amy Buskey-Wood
Photographers: Tom Merce, Russell Lee
Marketing: Samantha Brainard, Mindy Cannon, Suzanne Anthony, Kristin Swenson

Ob/Gyn & Women’s Health Perspectives is written for physicians and should be relied on for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

© 2018 The Cleveland Clinic Foundation

24/7 Referrals

855.REFER.123
(855.733.3712)
clevelandclinic.org/refer123

Outcomes Data

View Outcomes books at clevelandclinic.org/outcomes.

CME Opportunities

Visit ccfcmce.org for offerings from Cleveland Clinic’s Center for Continuing Education.
The Discussion of Fertility and Reproduction Options: A Core Component of Cancer Survivorship

By Rebecca Flyckt, MD

The Discussion of Fertility and Reproduction Options: A Core Component of Cancer Survivorship

Given the urgency of a cancer diagnosis, there may be limited time to talk about the impact lifesaving treatments can have on reproduction. Up to 75 percent of survivors are interested in having children after cancer treatments, yet few women are offered fertility preservation options. In our fertility practice, we see many women on the other side of cancer who grapple with lost fertility.

**Overcoming obstacles and misperceptions**

Only 2 percent of women with cancer pursue fertility preservation (compared with 60 percent of their male counterparts) due to multiple factors, including fear of delaying treatment. Lack of provider knowledge or understanding of a patient's wishes also can be a barrier. Clinicians may assume a patient wouldn't be interested in learning about fertility preservation because of her age (our patients have ranged in age from 4 to 45) or because she already has a child.

Another big deterrent to fertility preservation is financial burden. At Cleveland Clinic, we have established partnerships to assist with this and are encouraged by legislation (most recently, Illinois House Bill 2617 in August) requiring health insurance companies to cover the preservation of eggs, sperm and embryos for patients with cancer.

**Understanding fertility preservation options**

**Egg and embryo freezing** remain the gold standard. Huge advances have resulted in virtually no delay of cancer treatment. We can start treatment cycles within a day or two of referral and complete the fertility preservation cycle in two to three weeks. New, safe protocols reduce the risk of complications for cancer patients, and studies show that babies from egg and embryo freezing are healthy.

**Ovarian transposition** is a same-day, minimally invasive surgery performed prior to planned pelvic radiation. The procedure involves moving the ovary from its normal anatomic position out of the field of radiation. Ovary transposition has success rates in preserving ovarian function as high as 60 to 80 percent. Important to note, however, is that pelvic radiation may still have significant effects on the function of the uterus. Women exposed to pelvic radiation may stop having periods or may have pregnancy complications such as miscarriage, fetal growth restriction, early delivery or placental dysfunction. For that reason, uterine transposition is now available. This new option is designed to leave the uterus connected to its blood supply while positioning it outside of the pelvis temporarily during radiation treatments. It can then be moved back after treatments to a normal anatomic location for future pregnancy.

**Ovarian tissue vitrification** is an experimental procedure that involves removing one ovary along with its ovarian cortex, which is the portion of the ovary that contains the eggs. We vitrify and store very thin strips of the ovarian tissue with the possibility of reimplanting them into the pelvis after cancer treatment. This procedure has resulted in approximately 100 live births worldwide, many of which have been spontaneous (non-IVF) pregnancies. This is exciting technology with strong potential but is only being offered in the United States under an Institutional Review Board (IRB)-approved protocol. To date, we've frozen ovarian tissue primarily for prepubertal girls who didn't have the option of egg freezing.

**Gonadotrophin-releasing hormone antagonist (GnRHa)** is an injected hormone that can be given during chemotherapy to protect and preserve ovarian function. Halle Moore, MD, medical oncologist from Cleveland Clinic, has published landmark research in...
Case Study: A 36-year-old female with a history of acute myeloid leukemia (AML) became pregnant after being in clinical remission for several months. At 28 weeks' gestation, she had a routine blood count and a peripheral smear, which showed evidence of AML relapse. She was admitted to Cleveland Clinic for further evaluation and treatment. A lumbar puncture revealed leukemic involvement of the cerebral spinal fluid. An ultrasound of the fetus demonstrated that the baby was growing and developing normally.

Before recommending treatment, her multidisciplinary medical team had extensive discussions about the risks, benefits and alternatives, considering the impact on both mother and fetus. Her physicians agreed on immediate treatment of the relapse with chemotherapy (cytarabine and daunorubicin).

They also administered twice-weekly intrathecal chemotherapy via lumbar punctures. After allowing time for recovery from the effects of chemotherapy and further fetal maturity, labor was induced at approximately 34 weeks' gestational age, and she delivered a healthy baby girl. Her infant did well in the NICU following delivery.

The timing of the delivery allowed the mother to proceed with more definitive treatment for her leukemia. She continued intrathecal chemotherapy until the leukemic cells were cleared, and then one month after delivery, she underwent a bone marrow transplant. Both mother and child continue to do well more than a year later.

Cancer during pregnancy is more common than we think and is increasing. Why?

Dr. Chapa: Cancer affects about 1 in 1,000 pregnancies. The most common include breast cancer, cervical cancer, lymphoma/leukemia and melanoma. The incidence of malignancy increases with age, so the incidence of cancer during pregnancy is expected to rise since women are having children at older ages. As cancer treatments improve, more patients are surviving and with a higher quality of life after treatment. Thus, for women of childbearing age with a history of cancer, pregnancy is an increasingly common event.

What are some of the challenges involved in diagnosing cancer during pregnancy?

Dr. Chapa: Even during pregnancy, the standard oncologic diagnostic process should be used to obtain as much
In some cases, we can initiate treatment at an early stage of pregnancy and finish it after delivery for optimal results.

**How does cancer care during pregnancy impact patient outcomes?**

**Dr. Chapa:** It may surprise many Ob/Gyn specialists to learn that providing mothers with proper cancer care and evaluation during pregnancy actually yields better outcomes for both mothers and their babies. In fact, most cancer treatments don’t result in adverse pregnancy outcomes. Many babies can be delivered at or close to term and are healthy. It’s actually the exception that physicians would recommend delaying treatment or terminating the pregnancy. In general, avoiding or delaying treatment in pregnancy leads to additional health problems and complications for both mother and child.

**How do you balance using radiation or chemotherapy during pregnancy and protecting the fetus?**

**Dr. Chapa:** Radiation exposure early in a pregnancy can lead to miscarriage and birth defects. Later in a pregnancy, it can lead to developmental and neurological delays as well as microcephaly. With chemotherapy or radiation exposure, there’s also an increased risk of developing childhood malignancy after birth.

However, most cancer treatments are options during pregnancy, as long as we adjust the modality or timing. For example, some chemotherapy agents are safer to use than others. Also, oncologists usually avoid administering treatment during the final six weeks prior to delivery, since it can suppress the fetus’s immune system. During certain types of radiation treatment, radiation oncologists can shield the abdomen or adjust dosing so that radiation doesn’t reach the fetus.

In some cases, we can initiate treatment at an early stage of pregnancy and finish it after delivery for optimal results.

**What should a primary care physician or Ob/Gyn do when cancer is suspected in a pregnant patient?**

**Dr. Chapa:** It is essential to refer the patient to a center where there is skilled coordination between oncology and Ob/Gyn staffs. When planning cancer care for a pregnant patient, the Ob/Gyn and oncology teams must work together to develop an individualized plan that takes into account the type of cancer, cancer stage, prognosis, gestational age and patient preferences.
the small bowel, had metastasized to her liver and omentum. The median survival estimate is only several months for patients at a similar stage of the disease. Several hours after her liver metastectomy, tissue was implanted into a mouse. Within 10 days, a tumor with the histopathologic features of clear cell adenocarcinoma developed. By selecting cancers that grow aggressively, we can potentially develop PDX models in a time frame that is clinically actionable. In the Cleveland Clinic inventory of 220 PDXs derived from multiple cancer types, 5.3 percent of successfully generated PDX have been harvested within two weeks of implantation, suggesting that the experimental design can be expanded to other rapidly proliferating cancers.

Genomewide gene expression profiling showed high transcriptomic concordance of the matched donor tumor and the PDX. ERBB2 gene amplification was identified in the PDX, and the levels of ERBB2 mRNA in the PDX and primary tumor were similar. These data indicated high genomic fidelity between the PDX and the donor tumor.

Postoperative treatment
Following the patient’s surgeries, CT scans revealed new right inguinal lymphadenopathy, an enlarging right chest wall mass (separate from the area of resection) and an abdominal incisional recurrence, indicating widespread metastatic disease. The patient’s postoperative recovery allowed time to seek guidance from a multidisciplinary tumor board, which recommended the combination of nivolumab with cisplatin, gemcitabine or an anti-ERBB2 agent. After initial engraftment, the PDX was implanted into 12 mice representing these treatment cohorts. The PDX study indicated that the gemcitabine combination was the most effective at preventing tumor growth.

The patient ultimately received the combination of gemcitabine and nivolumab. In the third round of treatment in the PDX, progression was noted in one of the three mice. The treatment resistance was confirmed, and genetic testing showed that resistance was associated with gene expression changes that have been previously implicated in several classes of chemotherapeutics, including gemcitabine. After five cycles of therapy (five months), the patient demonstrated a partial response in all known sites of disease and no evidence of new lesions. However, soon afterward, as predicted by the PDX, the disease progressed to the perihilar region, the right chest wall, the right lateral abdominal wall musculature and the brain.

Second-line treatment and survival
Based on the results of another round of testing on the resistant PDXs, the patient received second-line treatment with concurrent paclitaxel with neratinib. She is alive with minimal residual disease 24 months past diagnosis, far longer than the average prognosis. Using the PDX model, we were able to prospectively predict the patient’s response to first-line therapy and identify the most optimal second-line therapy.

An NIH-funded follow-up study is in the works. It will randomize patients to avatar-directed or standard-of-care therapy and compare outcomes. We’re very excited about applying our avatar models to improve response rates in aggressive cancer types that have had very few advances in care. If we can even marginally improve the response rates for these generally recalcitrant tumors, that would represent a very significant advance for patients and their outcomes.

ABOUT THE AUTHORS

Dr. Abazeed is a clinician and researcher in Cleveland Clinic’s Departments of Translational Hematology Oncology Research and Radiation Oncology.
He co-authored this case study with Robert DeBernardo, MD, a gynecologic oncologist and Director of Minimally Invasive Surgery, and Roberto Vargas, MD, an Ob/Gyn who specializes in the surgical and chemotherapeutic management of women with gynecologic cancers.
Predictors of Lynch Syndrome and Clinical Outcomes Among Universally Screened Endometrial Cancer Patients

By Caitlin Carr, MD; Milena Radeva; Anju Priyadarshini, MD; Jessica Marquard, MS, LGC; and Mariam Alhilli, MD

Lynch syndrome (LS) is a highly penetrant, autosomal dominant inherited cancer condition responsible for most hereditary endometrial and colorectal cancers. This condition is caused by inherited mutations in the four mismatch repair (MMR) genes — MLH1, MSH2, MSH6 and PMS2 — ultimately leading to DNA microsatellite instability (MSI).

Universal screening using MSI and/or immunohistochemistry for LS in colorectal cancer is widely established in the United States and is currently a CDC tier 1 genomic application. However, the acceptance of universal tumor testing in endometrial cancer (EC) has come much more slowly, even though the Society of Gynecologic Oncology recommends molecular screening as the preferred strategy.

At Cleveland Clinic, implementation of universal screening for EC, initiated in 2012, has allowed for characterization of LS patients in one of the largest prospective cohorts of screened patients. This database provides fertile ground for generalizability and further information regarding the relationship between MMR classification and clinicopathologic characteristics suggestive of LS.

Utilizing data from 723 patients who underwent tumor testing with IHC analysis, we identified defects in MMR proteins. Patients with intact MMR expressed were considered to have sporadic EC. Those with absent MMR proteins and negative for MLH1 methylation (N = 33) were considered LS-suggestive and were offered genetic counseling and germline testing for definitive diagnosis of LS.

A look at our findings

On multivariate analysis utilizing LS-suggestive tumors as the reference characteristic, we found that those patients suggestive of LS were of younger age and had a lower BMI than patients with MMR-intact tumors. LS-suggestive tumors were also higher grade, of endometrioid histology, < 2 cm in size and more likely to have greater than 50 percent invasion into the myometrium. These findings are in line with previous work.

Interestingly, family history of first-degree or second-degree LS-associated tumors, positive lymphovascular space invasion (LVSI), International Federation of Gynaecology and Obstetrics stage, race, parity and menopausal status were not associated with suggestive LS. Substantial myometrial invasion and higher histological grading have been highly associated with poorer prognostic features; however, we found no difference in overall survival or recurrence-free survival (RFS) between those suggestive of LS and those patients with MMR-intact tumors.

We also found that age-based screening protocols would have overlooked 30.8 percent of confirmed LS patients had these protocols maintained 60 as their age limit. In addition, the revised Bethesda criteria included only one of the LS-suspicious patients and none of those with germline diagnosis, reinforcing the need for universal screening for LS in EC patients.

Reinforcing need for universal screening

ECs with MLH1 hypermethylation are associated with known adverse prognostic factors, including older age, higher grade, LVSI and myometrial invasion > 50 percent. These tumors have a higher rate of recurrence overall (including in patients with early-stage disease) and a significantly lower RFS versus sporadic EC, raising an important question regarding the possible utilization of universal IHC tumor testing for purposes outside of LS detection. MLH1 methylated status appears to be an important prognostic factor to consider in patient counseling and treatment decision-making in endometrial cancer.

ABOUT THE AUTHORS

Dr. Alhilli is an Ob/Gyn in the Ob/Gyn & Women’s Health Institute.

Dr. Carr is a resident (PGY3) with a concentration in gynecologic oncology. Dr. Priyadarshini is a pathobiology research scholar. Ms. Radeva is a senior biostatistician in Qualitative Health Sciences. Ms. Marquard is a genetic counselor in the Genomic Medicine Institute.
The Cleveland Clinic Foundation
9500 Euclid Ave. / AC311
Cleveland, OH 44195

The Increasing Mortality Rate for Pregnant Women in the U.S.

Why this is happening and what to do about it — right now

“More women die from pregnancy complications in the United States than in any other developed country,” reports the American College of Obstetricians and Gynecologists (ACOG), and the U.S. is the only industrialized country in which the maternal mortality rate is rising. OB/Gyn & Women’s Health Perspectives talked with Uma Peri, MD, about this disturbing trend.

Why is the maternal death rate increasing?
Dr. Peri: The maternal mortality rate in the U.S. increased by more than 25 percent between 2000 and 2014. This increasing mortality rate among pregnant women is quite alarming for OB/Gyn providers. The problem is multifactorial. There are a number of social issues, such as drug overdoses and suicide, but chronic disease and obesity play a role too. Women with pre-existing medical conditions such as diabetes and hypertension are at higher risk if they become pregnant. Pre-existing cardiac conditions in pregnant women account for approximately 20 percent of maternal mortality in the U.S.

In the 1980s, when maternal mortality rates were at their lowest, certain types of chronic diseases we have today occurred at much lower rates in pregnant women — hypertension, diabetes, obesity. And many women with heart disease and other conditions did not survive to child-bearing age. In addition, women today are often delaying childbearing to a later age.

We still see deaths from long-known causes of maternal mortality such as pre-eclampsia, uterine hemorrhage and infection.

So there are a host of reasons for the increasing incidence of maternal morbidity and mortality.

What about racial disparities in these statistics?
Dr. Peri: The other very shocking statistic is the racial disparity we see in maternal mortality. The fact that African-American women have a greater than three times higher rate of death than their Caucasian counterparts is shocking and distressing. There are many theories for why this occurs, including socioeconomic factors, access to care and chronic stress. However, even if we just look at white women in the U.S., maternal mortality rates are higher than in other developed countries.

Cleveland and Ohio are no different and also display the shocking national trends of increasing maternal mortality and racial disparities. Ohio has established a Pregnancy-Associated Mortality Review (PAMR), a multidisciplinary group of experts who reviewed these cases and develop initiatives to prevent future maternal deaths.

What can be done?
Dr. Peri: One of the things we see is women getting pregnant who are at very high risk of dying due to their underlying medical conditions. For example, women with pulmonary hypertension, cardiomyopathy and other pre-existing medical conditions are risking their lives by getting pregnant. They often become pregnant because they have not been counseled appropriately, and then it is sort of too late.

This is where we have a huge opportunity for intervention. These women — prior to becoming pregnant — need to be counseled about birth control and the real risks they will face should they become pregnant.

This is an overlooked opportunity and something that has real potential to positively impact the maternal mortality rate.

Dr. Peri is an OB/GYN in Cleveland Clinic’s OB/GYN & Women’s Health Institute.

Read the entire interview at consultqd.
clevelandclinic.org/maternalmortality.