



Ob/Gyn & Women's Health Perspectives

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

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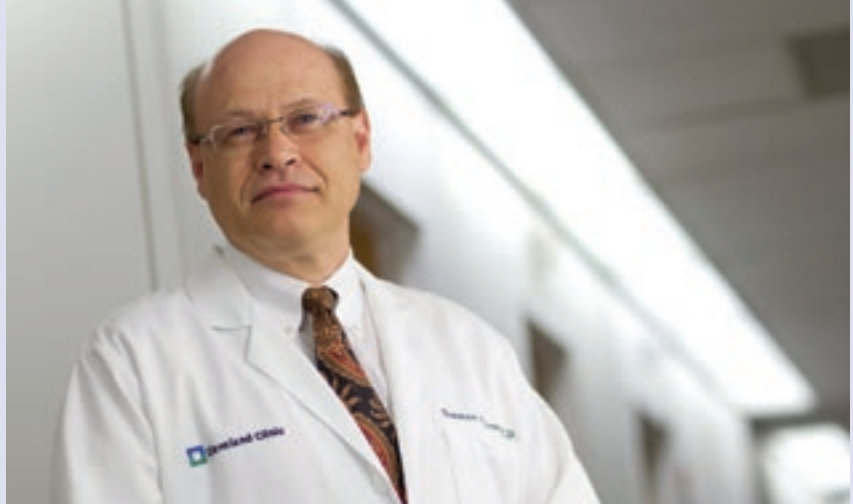




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Dear Colleagues and Friends:

There is no shortage of controversies in the field of women's health. Several of the articles in this issue of *Ob/Gyn & Women's Health Perspectives* address issues that may, for one reason or another, be viewed from strongly contrasting angles.

One example is the article by Stephanie Ricci, MD, on tissue extraction by means of open electromechanical morcellation. Reports on a device widely used in this procedure led the FDA to issue a "black box" warning for the device in 2014. Dr. Ricci suggests that while the initial concerns were legitimate, the FDA may have drawn inaccurate conclusions from limited data. She makes a compelling case for a review of the FDA's conclusions.

What the public now calls gender reaffirmation surgery is, we are pleased to note, becoming less controversial as time goes by. Mixed opinions about these surgeries have historically led to their being limited in availability and rarely taught at major medical centers. As Cecile Unger, MD, MPH, reports, Cleveland Clinic gynecological surgeons performed eight male-to-female procedures in 2016 and look forward to expanding our practice in this area. Outcomes are being closely monitored to provide data for quality and safety improvement. We are cheered by the promise that gender reaffirmation surgery may soon be moving into the academic realm.

I myself am pleased to offer my considerations on the management of ovarian cysts, a topic on which expert views may vary. Here, the controversies are more technical, but still a critical part of the conversation when speaking with patients concerned for their health and fertility.

I also provide an overview of findings from a recent study that examined whether the presence of an intrinsic endometrioma is associated with decreased ovarian reserve, and whether its surgical removal decreases reserve further.

Cleveland Clinic is proud to be ranked No. 3 in America for Ob/Gyn in "America's Best Hospitals" (*U.S. News & World Report*). Thank you for your ongoing interest in our programs. We appreciate your referrals and look forward to treating your patients and returning them to your care.

Tommaso Falcone

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Perioperative Management of the Transgender Patient

By Cecile Unger, MD, MPH

In 2016, eight genital surgeries for transgender women were successfully performed at Cleveland Clinic. I perform one to two of these surgeries per month, with the assistance of the female pelvic medicine and reconstructive surgery fellows as well as the Ob/Gyn residents.

Our program has grown very busy as a result of improved commercial and government-sponsored insurance coverage for transgender-specific services. We are now booking into June 2017.

Previously referred to as “sex reassignment surgery,” male-to-female vaginoplasty or “gender affirmation surgery” is currently performed by about a dozen U.S. surgeons. Historically, private practice surgeons performed these procedures, and training was obtained through apprenticeships. Efforts are now underway to move this surgical subspecialty into the academic realm, and fellowship programs are in development.

How our program is set up

At Cleveland Clinic, patients undergo surgical consultations at one of three sites in Greater Cleveland. Our team follows the World Professional Association for Transgender Health guidelines to ensure patients are appropriate surgical candidates.

We require that patients live full time as their self-affirmed gender for more than one year, that they have undergone cross-sex hormone therapy for at least one year, and that they have two letters of support for surgical transition from two mental health professionals who are well-versed in transgender patient care. Patients who have met these criteria are deemed appropriate surgical candidates.

They cannot be smokers or be excessively overweight, and they must be medically optimized for surgery if they have medical comorbidities.

A closer look at the procedure

The approximately four- to five-hour surgery is performed at Cleveland Clinic’s main campus, using the penile inversion vaginoplasty technique. This involves use of the penile skin and a scrotal graft to create a functional neovaginal tube, which is inset in the vesicorectal space, a potential space that is created through a transperineal dissection. The external genitalia are created using penile skin, a portion of the urethral mucosa and the penile structures including the glans penis.

Postoperatively, the reconstructed anatomy is functional and sensate. Surgical risks include bleeding and need for transfusion; postoperative hematoma, seroma and infection; and intraoperative rectal, bladder and urethral injury, with risk for postoperative fistula formation between these organs and the neovagina. Patients are well-counseled preoperatively regarding these risks, including an extensive discussion regarding expectations for cosmetic and functional outcomes.

Patients are admitted to the hospital for three nights and remain on bedrest, allowing their flaps to heal prop-

erly. They are closely monitored and discharged on postoperative day three to an on-campus hotel, where they are observed for four to 10 nights.

Length of stay depends on how far they have traveled. Six of our eight patients were from out of state and required extended recovery time before returning home. Nonlocal patients must have a nearby provider who has agreed to help with any necessary postoperative care. This allows constant communication to ensure that patients are healing properly and getting needed wound care to guarantee favorable outcomes.

Continued growth anticipated

We look forward to our program expanding. Each month, our volume of patients from Greater Cleveland and beyond increases.

Integrating surgical care for transgender women into our training programs is becoming a priority, and we plan to develop a research initiative to help track outcomes and advance this surgical subspecialty.

ABOUT THE AUTHOR



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Uterine Morcellation: Can We and Should We?

By Stephanie Ricci, MD

Uterine tissue extraction using open electromechanical morcellation has been called into question in recent years.

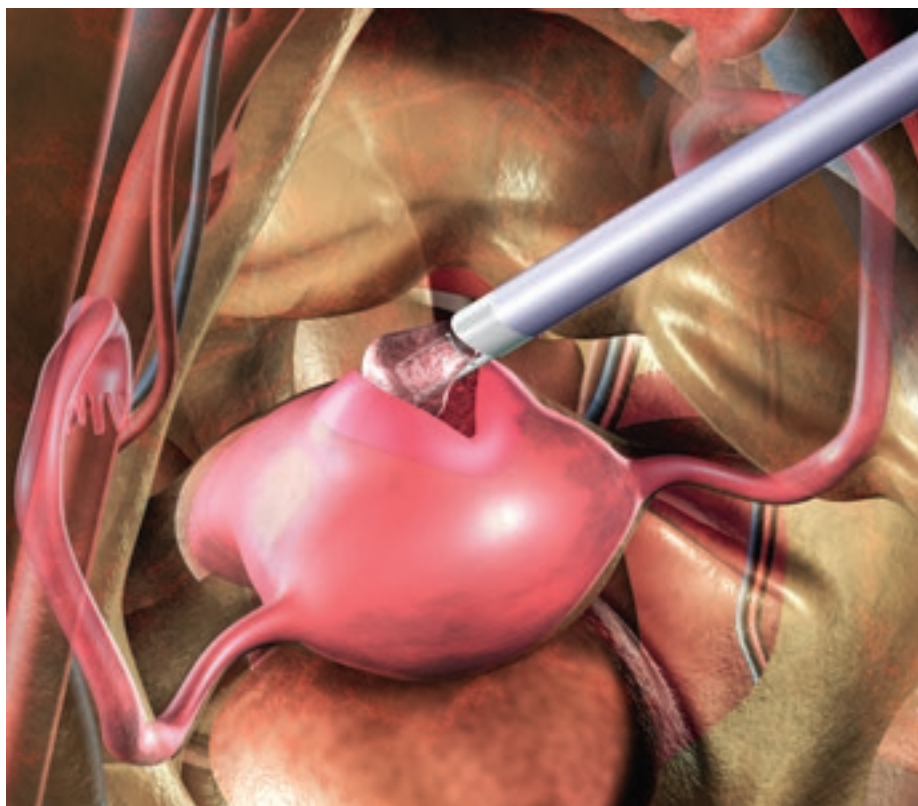
Much of the controversy surrounding use of a laparoscopic power morcellation device stemmed from the concern that selected women with presumed benign disease may undergo a uterine and tissue extraction procedure that results in disruption, and possible dissemination, of a malignant tumor.

In April 2015 the Food and Drug Administration (FDA) issued a safety communication discouraging the use of the technique for minimally invasive hysterectomy and myomectomy in patients with benign conditions. An advisory committee continues to examine the issue.

In the meantime, unanswered questions

Does uterine morcellation of an occult leiomyosarcoma (LMS) increase recurrence risk and reduce survival? Several small studies have attempted to answer this question. Most compared women with uterine-confined LMS at the time of surgery, divided into intact versus fragmented removal. It is important to note that all methods of fragmentation were used in these studies, including vaginal and abdominal hand morcellation as well as electromechanical morcellation.

One study compared 25 patients who underwent morcellation to 31 patients with intact tumor removal. They found a higher rate of abdominopelvic dissemination (44 percent versus 12.9 percent, $P = 0.032$) and poorer overall survival on multivariate analysis in the morcellated cohort.



Another study compared 19 women with fragmented uterine removal and 39 with intact removal and reported a threefold increase in risk of recurrence in the morcellation cohort. Researchers did not, however, note a difference in overall survival.

Interestingly, a third study, which included hysteroscopic myomectomy in its “tumor injury” cohort, similarly found significantly better survival rates and decreased recurrence rates for women undergoing intact removal of the uterus. Another study demonstrated a high rate

of recurrence (70.8 percent) for women with apparent uterine-confined, non-morcellated LMS that rivaled the recurrence rates noted in the studies above in morcellated cases.

Given that existing studies are retrospective and not powered to detect differences in recurrence or survival for women with LMS who have their uteri removed intact versus morcellated, no conclusions can be made regarding the impact of open electromechanical morcellation on the survival outcomes of these women.

At Cleveland Clinic

At our institution, we have taken a cautious and conservative approach to morcellation. We still perform hand-assisted uterine fragmentation, either through the vagina or a mini-laparotomy, in carefully selected women after extensive counseling, comprehensive pre-operative workup and informed consent.

We employ the following patient-selection criteria:

- Imaging (MRI for fibroids)
- Endometrial evaluation
- Exclusion criteria for morcellation
 - Age > 50
 - History of tamoxifen use
 - Pelvic radiation
 - BRCA mutation carrier status
 - Hereditary cancer syndromes

- Enhanced surgical consent
- High-volume surgeons only
- Hand morcellation only

We feel these guidelines help produce safe, low-risk, excellent outcomes for our patients.

SUGGESTED READING

1. Park JY, Park SK, Kim DY, et al. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. *Gynecol Oncol.* 2011;122(2):255-259.
2. George S, Barysaukas C, Serrano C, et al. Retrospective cohort study evaluating the impact of intraperitoneal morcellation on outcomes of localized uterine leiomyosarcoma. *Cancer.* 2014;120(20):3154-3158.
3. Perri T, Korach J, Sadetzki S, Oberman B, Fridman E, Ben-Baruch G. Uterine leiomyosarcoma: does the primary surgical procedure matter? *Int J Gynecol Cancer.* 2009;19(2):257-260.

ABOUT THE AUTHOR



Dr. Ricci is an associate staff member in the Department of Obstetrics and Gynecology. She can be reached at 216.445.1002 or riccis@ccf.org.

Table. Major studies reporting on the incidence of occult uterine sarcoma and LMS

Author	Year published	Total patients	Number of uterine sarcomas	Rate of uterine sarcoma	Number of LMSs	Rate of LMS
Parker et al.	1994	1,332	3	2.3	1	0.8
Pritts et al.	2015	30,193	NR	NR	3	0.002
Raine-Bennett et al.	2016	34,728	125	0.36	NR	NR
Lieng et al.	2015	4,791	NR	NR	6	0.1
Mahnert et al.	2015	6,360	12	0.2	NR	NR
Kho et al.	2016	10,119	9	0.09	NR	NR

LMS = leiomyosarcoma, NR = not reported

Understanding the Effect of Surgery on Ovarian Reserve in Women with Endometriomas and Endometriosis

By Tommaso Falcone, MD

Endometriomas are one of the most common ovarian cysts. These may be associated with pelvic pain or infertility. Surgical removal is common. There are several controversies surrounding the management of these cysts.

For example, the removal of an endometriotic cyst is known to improve spontaneous fertility, but it may not improve outcomes with in vitro fertilization. In any event, it is unclear whether the presence of the cyst or its removal is associated with decreased ovarian reserve (loosely defined as the quantity of oocytes remaining in the ovary). There are several potential measures for ovarian reserve, of which anti-müllerian hormone (AMH) is the most frequently used.

Study design

Our group recently published a study¹ in which we posed two questions: Is the presence of an intrinsic endometrioma associated with decreased ovarian reserve, and does its surgical removal decrease reserve further? This was a prospective study of women aged 18 to 43 years presenting with pelvic pain and/or infertility undergoing surgical management for suspected endometriosis (N = 58) or endometriomas (N = 58). Based on surgical findings, the suspected endometriosis group was further separated into those with evidence of peritoneal disease (N = 29) and those with no evidence of endometriosis (N = 29).

Highlights of our findings

Baseline AMH values were significantly lower in the endometrioma group versus the negative laparoscopy group. Only

patients with endometriomas had a significant decline in ovarian reserve at one month. Six months after surgery, AMH hormone values were no longer significantly different from baseline, demonstrating some recovery from surgery.

We concluded that, at baseline, patients with endometriomas had significantly lower AMH values compared with women without endometriosis. Surgical excision of endometriomas appears to have temporary detrimental effects on ovarian reserve. Clinically, this means that we should consider carefully the long-term impact on fertility when we remove an endometrioma.

REFERENCE

1. Goodman LR, Goldberg JM, Flyckt RL, Gupta M, Harwalker J, Falcone T. Effect of surgery on ovarian reserve in women with endometriomas, endometriosis and controls. *Am J Obstet Gynecol.* 2016;215(5):589.

ABOUT THE AUTHOR



Dr. Falcone is Professor and Chairman of the Department of Obstetrics and Gynecology and Chairman of the Ob/Gyn & Women's Health Institute. He can be reached at 216.444.1758 or falcont@ccf.org.

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The Potential Role of Gonadotropin-Releasing Hormone Agonists in Preserving Gonadal Function in Women Undergoing Chemotherapy

By Tommaso Falcone, MD

A diagnosis of cancer is a life-changing event. There are so many aspects of this disease that must be considered, one of which is quality of life associated with preservation of ovarian function.

Preserving ovarian function is important not only to safeguard fertility, but also to maintaining quality of life and preventing medical consequences. For example, the hormonal changes that often accompany loss of ovarian function can affect sexual function and lead to psychological stress and relationship strain. Alterations in hormonal function may also lead to early menopause symptoms, osteoporosis and cardiovascular disease.

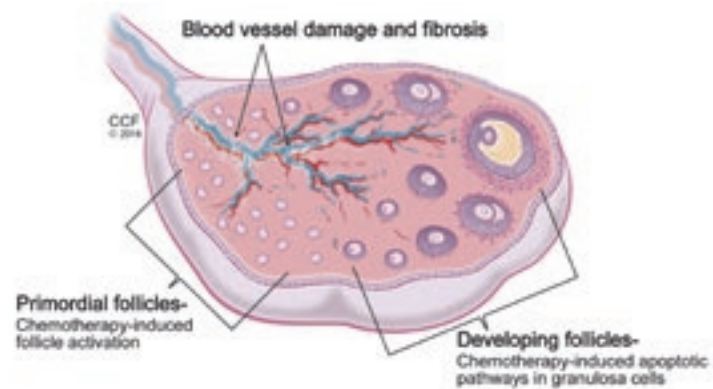


Figure. Proposed mechanisms for chemotherapy effect on ovarian follicles
Chemotherapy causes ovarian damage by both direct and indirect mechanisms.

Nonexperimental options

In our review,¹ we highlighted the options women have for preserving ovarian function while undergoing chemotherapy. For preservation of fertility, we offer in vitro fertilization with egg or embryo freezing, if the patient has a partner. These forms of treatment are not considered experimental.

New ovarian stimulation protocols can be initiated immediately to avoid delaying chemotherapy. Furthermore, aromatase inhibitors can be used to decrease estradiol levels in women with estrogen-sensitive tumors such as breast cancer.

Additional investigational offerings

Experimentally, we can offer ovarian tissue cryopreservation and subsequent autotransplantation when the medical oncologists deem that the disease is in remission. The advantage of this procedure is that it can be done immediately

with no delay in treatment, an option that is appealing for patients whose tumors require instantaneous treatment.

None of these treatments, however, protect gonadal function long term. Even with autotransplantation, the longevity of the graft is generally only a few years, although it may be longer.

Best-case scenario

The ideal scenario is one in which the patient receives a drug that blocks the effects of chemotherapy on the most sensitive ovarian cells — the primordial follicles. For the moment, the only drug available is a gonadotropin releasing-hormone agonist such as leuprolide acetate.

The use of this drug is controversial because it traditionally is used to suppress the hypothalamic-pituitary-ovarian axis rather than to protect the ovaries from the effects of chemotherapy. We

reviewed the evidence that supports this latter use, especially in breast cancer patients. Although leuprolide acetate is considered experimental for this indication, it is the only one available that can potentially protect gonadal function in women undergoing chemotherapy.

REFERENCE

1. Hickman LC, Valentine LN, Falcone T. Preservation of gonadal function in women undergoing chemotherapy: a review of the potential role for gonadotropin-releasing hormone agonists. *Am J Obstet Gynecol.* 2016;215(4):415-422.

ABOUT THE AUTHOR



Dr. Falcone is Professor and Chairman of the Department of Obstetrics and Gynecology and Chairman of the Ob/Gyn & Women's Health Institute. He can be reached at 216.444.1758 or falcont@ccf.org.

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