RELIAS MEDIA

Vol. 36, Issue 6, October 2019
ReliasMedia.com

OB/GYN Clinical [ALERT]

Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Diagnostic Imaging Trends Among Pregnant Women

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Dr. Allen reports she receives grant/research support from Bayer and is a consultant for Merck.

SYNOPSIS: This retrospective cohort study estimated that the use of CT scans has increased 3.7-fold in the United States and 2-fold in Ontario, Canada, from 1996 to 2016. Overall, 5.3% of pregnant women in the United States and 3.6% in Ontario underwent imaging with ionizing radiation.

SOURCE: Kwan ML, Miglioretti DL, Marlow EC, et al. Trends in medical imaging during pregnancy in the United States and Ontario, Canada, 1996-2016. *JAMA Netw Open* 2019;2:e197249.

This retrospective cohort study was performed at six U.S. healthcare systems (Kaiser Permanente of Northern California, Northwest, Washington, and Hawaii; Marshfield Clinic in Wisconsin; and Harvard Pilgrim in Massachusetts) and in Ontario, Canada, to evaluate radiology exposures in pregnant women between Jan. 1, 1996, and Dec. 31, 2016. Eligible women were required to be enrolled in the health system for their entire pregnancy and had to give birth to a neonate of at least 24 weeks' gestational age. Dates and types of all imaging studies performed during the pregnancy were collected, including computed tomography (CT), magnetic resonance imaging (MRI), radiography, angiography, fluoroscopy, nuclear medicine, and ultrasound. Imaging procedures performed for radiation treatment for cancer or with biopsies were excluded.

A total of 3,497,603 pregnancies from 2,211,789 women were included, with 26% from U.S. sites. Overall, 5.3% of patients from U.S. sites and 3.6% in Ontario underwent imaging with ionizing radiation and 0.8% in U.S. sites and 0.4% in Ontario underwent CT. In U.S. sites, CT use rates increased from 2.0 studies per 1,000 pregnancies

Financial Disclosure: *OB/GYN Clinical Alert*'s Editor Jeffrey T. Jensen, MD, MPH, reports that he is a consultant for and receives grant/research support from ObstetRx, Bayer, Merck, and Sebela; he receives grant/research support from AbbVie, Mithra, and Daré Bioscience; and he is a consultant for CooperSurgical and the Population Council. Peer Reviewer Catherine Leclair, MD; Nurse Planner Marci Messerle Forbes, RN, FNP; Editorial Group Manager Leslie Coplin; Editor Jason Schneider; and Executive Editor Shelly Mark report no financial relationships relevant to this field of study.

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OB/GYN Clinical Alert (ISSN 0743-8354) is published monthly by Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468. Periodicals postage paid at Morrisville, NC, and additional mailing offices. POSTMASTER: Send address changes to *OB/GYN Clinical Alert*, Relias LLC, 1010 Sync St., Ste. 100, Morrisville, NC 27560-5468.

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in 1996 to 9.3 studies per 1,000 pregnancies in 2016 (3.7-fold). The use of chest CT, in particular, increased in U.S. sites from 0.2 per 1,000 to 4.0 per 1,000 pregnancies. The rate of MRI use also increased in the United States from one study per 1,000 pregnancies in 1996 to 11.9 per 1,000 pregnancies in 2016. The use of MRI for the abdomen and pelvis increased the most, from 1.1 per 1,000 pregnancies to 5.5 per 1,000 pregnancies. Radiography, angiography, fluoroscopy, and nuclear medicine imaging rates remained stable over time.

■ COMMENTARY

The authors of this study used health system records to estimate the increase in the use of imaging studies among pregnant women over a 21-year period in the United States and Canada. There are some limitations, in that only pregnant women who had a live birth greater than 24 weeks' gestation were included, and researchers did not have information on the indications for the studies. However, the data do provide reliable information regarding the trend in imaging use over time using multiple sites that are attributed likely generalizable. The authors attribute this increase to multiple potential causes, such as advances in imaging technology, patient and physician demand, and defensive medicine.

The use of X-rays and CT scans involves ionizing radiation, and the risk to the fetus depends on the gestational age and dose of radiation. The threshold dose for causing congenital anomalies during the period of organogenesis (4 to 10 weeks' gestational age) is estimated at 200 mGy. The dose for causing intellectual disability at 10 to 17 weeks' gestational age is estimated at 60 to 310 mGy.[1] A chest X-ray with two views exposes the fetus to only 0.0005 to 0.01 mGy. A chest CT exposes the fetus to 0.01 to 0.66 mGy, and a pelvic CT approaches 2.5 to 50 mGy. The exposure from CT can be modulated by the number and spacing of the images. Given these numbers, the use of chest CT for the evaluation of pulmonary embolus in pregnant women is appropriate. According to this study, chest CT for this indication has become more popular in the United States than the traditional ventilation-perfusion scanning compared to Ontario, Canada. While iodinated intravenous contrast for CT scans has not been shown to be harmful to the fetus, it is recommended for use only if absolutely needed.[2]

As this study shows, the use of MRI, especially for the abdomen and pelvis, has increased in pregnant women over time and surpasses the use of CT. MRI has the advantage of not using ionizing radiation and is considered safe for the fetus. MRI can be used in the evaluation of acute appendicitis in pregnancy or for placenta accreta, especially if ultrasound is unable to provide the detail necessary. Unlike CT, MRI typically can visualize structures without the use of contrast. The use of gadolinium-based contrast, when needed for additional imaging,

[The use of X-rays and CT scans involves ionizing radiation, and the risk to the fetus depends on the gestational age and dose of radiation.]

has been controversial in pregnancy. Gadolinium is water-soluble and can cross the placenta and enter the fetal circulation and amniotic fluid. It is administered in a chelated form because free gadolinium is toxic. The duration of fetal exposure to gadolinium is of concern because it may disassociate into a free form the longer it remains in the amniotic fluid. Nevertheless, the American College of Obstetricians and Gynecologists states that gadolinium can be used if it is expected to improve interpretation of the MRI significantly and will benefit maternal or fetal outcome.[2]

During the course of caring for pregnant women, diagnostic imaging studies sometimes are necessary to assist with the evaluation of acute and chronic conditions. While the overuse of diagnostic imaging should be avoided, it is also important not to unnecessarily restrict access to studies that are needed, even if a woman is pregnant. Ultrasound and MRI avoid ionizing radiation and typically are not restricted in pregnancy. X-rays expose the fetus to minimal

amounts of radiation. CT scans of the abdomen and pelvis are of the most potential concern depending on the settings used, but even these might be indicated for maternal health. Overall, providers should be judicious in their recommendations for diagnostic imaging tests and only use them if benefit to the patient will result. ■

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ABSTRACT & COMMENTARY

Does Vaginal Estradiol Reduce Pain With Sexual Activity?

By Jeffrey T. Jensen, MD, MPH, Editor

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Dr. Jensen reports he receives grant/research support from and is a consultant for ObstetRx, Bayer, Merck, and Sebela Pharma; is a consultant for AbbVie, Mithra, and Daré Bioscience; and receives grant/research support from CooperSurgical and the Population Council.

SYNOPSIS: A post-hoc analysis of data from a 12-week randomized study that compared vaginal estradiol to vaginal moisturizers found no increase in sexual frequency or decrease in pain associated with either treatment, compared to placebo.

SOURCE: Mitchell CM, Guthrie KA, Larson J, et al. Sexual frequency and pain in a randomized clinical trial of vaginal estradiol tablets, moisturizer, and placebo in postmenopausal women. *Menopause* 2019;26:816-822.

In this paper, Mitchell and colleagues report results from a secondary post-hoc analysis of data from a previously published double-blind placebo-controlled trial. That study randomized postmenopausal women with moderate to severe genitourinary discomfort to vaginal treatment with a vaginal estradiol tablet, vaginal moisturizer, or placebo.[1] Women used the vaginal tablet daily for two weeks, and then twice weekly for 10 weeks; they used the gel every third day throughout the trial (total 12 weeks of therapy). The treatment groups included an active vaginal estrogen tablet (Vagifem, 10 mcg estradiol) plus a placebo (hydroxy-methylcellulose) gel, a placebo tablet plus an approved vaginal moisturizer (Replens; contains purified water, glycerin, mineral oil, polycarbophil, carbomer homopolymer type B, hydrogenated palm oil glyceride, sorbic acid, and sodium hydroxide), or dual placebo (tablet and gel).

The primary outcome of the original randomized study was a change in severity of the most bothersome symptom (MBS) between enrollment and weeks four and 12. The MBS was defined by the participant at trial enrollment as either vulvovaginal itching, pain, dryness, irritation, or pain with penetration, with severity rated as none, mild, moderate, or severe on a 0 to 3 scale. The investigators found similar mean reductions in MBS severity over 12 weeks with both active treatments and placebo.

This new secondary analysis was intended to evaluate the effect of treatment on the frequency of sexual activity and on the pain severity with sexual activity. The study population of 302 women (102 received the estradiol tablet, 100 received the active gel, and 100 received placebo) had 80% power to detect a 22% difference in these outcomes with a 5% alpha error. The mean age of participants was 61 years; most were white (88%), college-educated (66%), and most reported sexual activity in the month before enrollment (81%).

After 12 weeks of therapy, similar proportions of women in the vaginal estrogen (49.5%, [95% confidence interval, 39.1, 59.8]), vaginal gel (35.2% [25.2, 45.2]), and dual placebo (39.8 [29.7, 49.9]) groups reported sexual activity in the past week. The mean pain scores with sexual activity at 12 weeks also did not differ between groups. Based on these results, the authors concluded that a 12-week treatment course of low-dose vaginal estradiol or commercial vaginal moisturizer treatment did not result in a significant improvement in the frequency of sexual activity or the pain scores in postmenopausal women.

■ COMMENTARY

Another published study found no benefit of hormonal therapy on sexual function in postmenopausal women — or did it?

While it is well-established that vulvovaginal atrophy accompanies the increase in sexual discomfort associated with postmenopausal hypoestrogenism, and that hormonal therapy (HT) improves symptoms of genital atrophy, the impact of postmenopausal hormonal therapy on sexual function remains an area of ongoing controversy. Much of the problem comes from study design and the difficulty of assessing the right outcomes. We must critically assess the limitations of studies evaluating sexual health to better serve the needs of postmenopausal patients.

Recently I reported on an analysis of data from the Women's Health Initiative Study (WHI) that evaluated sexual activity following discontinuation of therapy.[2] This study found no difference in the prevalence of sexual activity postintervention between former participants randomized to hormonal therapy (36%) and placebo (34%, $P = 0.37$). However, women in the study who had received active hormonal treatment during the intervention period were significantly more likely (20%) to report a decreased frequency of intercourse postintervention than the group formerly randomized to placebo (9%), and also were more likely to report decreases in desire (17% vs. 6%), arousal (17% vs. 7%), ability to orgasm (19% vs. 7%), and satisfaction with sexual activity (17% vs. 8%), as well as increases in the tightness of the vagina (12% vs. 3%) and discomfort with intercourse (15% vs. 3%). Furthermore, sexual activity reported by former hormonal therapy users following discontinuation was 5.6% higher than sexual activity reported by placebo users (27.6% vs. 22.0%; $P < 0.001$). The results suggest that changes in sexual function occur over time in postmenopausal women, with hormonal therapy associated with modest protection.

It is also possible that women accommodate vaginal symptoms by avoiding intercourse. Compared to women randomized to estrogen, significantly fewer former placebo users (37% vs. 44%) reported having had sex after the WHI, and those who did reported a significant decrease in the frequency of sex with a partner postintervention.

The Mitchell papers provide similar hints that estrogen makes a difference. Significantly more women randomized to vaginal estradiol reported penetrative sex in the past week (43.5%; 33.2, 53.8) compared to the vaginal gel (33.0%; 23.1, 42.8). While the comparison with the dual placebo did not quite reach statistical significance (34.8% [24.9, 44.7]), the trend is the same. Women who received estrogen also showed improvement in vaginal maturation scores and a lowering of vaginal pH. While the overall comparison did not suggest that estrogen treatment resulted in a decrease in pain, the overall pain scores reported by women were low in all groups. Of great interest is the fact that many women did not report a score for sexual pain, presumably because they were not engaging in penetrative sex. Once again, we see a single efficacy with hormonal therapy; compared to placebo, more women who received estrogen reported a score for pain with sexual activity.

To be fair, a strength of the Mitchell paper is the use of patient-centered outcomes. However, we need to really consider if 12 weeks of therapy reflect reality. Treatment of vaginal symptoms also may require an emphasis on prevention; starting vaginal therapy a decade after menopause (the mean age of participants in this study was 61 years) simply may be too late. ■

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ABSTRACT & COMMENTARY

Association Between Self-Reported Prenatal Cannabis Use and Maternal, Perinatal, and Neonatal Outcomes

By Camille Hoffman, MD, MSc

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Dr. Hoffman reports no financial relationships relevant to this field of study.

SOURCE: Corsi DJ, Walsh L, Weiss D, et al. Association between self-reported prenatal cannabis use and maternal, perinatal, and neonatal outcomes. *JAMA* 2019;322:145-152.

SYNOPSIS: Cannabis use during pregnancy has become commonplace in states and countries (Canada) where it has been legalized for medical and/or recreational use. The authors of this study attempted to determine whether associations exist between self-reported prenatal cannabis use and maternal and perinatal outcomes.

In a cohort of more than 650,000 women in Ontario, Canada, 9,428 (1.4%) reported cannabis use during pregnancy at the first prenatal care visit and/or upon admission to labor and delivery. The authors then matched 5,639 of the reported cannabis users with 92,873 pregnant women who did not report cannabis use. Both groups had complete information available for confounders, including maternal age, parity, income, pre-pregnancy BMI, maternal smoking (tobacco), alcohol use, opioid use, and psychiatric disorders.

The primary outcome was preterm birth rate < 37 weeks. Other preterm birth (PTB) groupings (e.g. 34-36 6/7, 28-31 6/7, < 28 weeks) were also assessed, as were other obstetrical outcomes including abruption, small for gestational age (SGA) at birth, preeclampsia, and gestational diabetes.

In matched cohort analyses, PTB < 37 weeks was 1.41-fold higher (95% confidence interval [CI], 1.36-1.46) in women who reported cannabis use than in those who did not. After separating the PTB groupings, there was a categorical increase in PTB in both groups by both a risk difference (RD) calculation and using relative risk (RR) of PTB: 34-36 6/7 weeks, RD 1.75% and RR 1.31, to 28-31 6/7 weeks, RD 0.68% and RR 2.42. There was no difference in PTB < 28 weeks, although overall numbers were small. RD and RR are reported here to give the reader a sense of how distorted RR can be when overall numbers are small.

Interestingly, there was a significant (albeit not clinical) risk difference in preeclampsia and gestational diabetes favoring the cannabis-using group. Cannabis use was not associated with cesarean delivery or operative vaginal delivery risk. On the other hand, cannabis use was associated with SGA less than the third percentile (6.1% vs. 4.0%), abruption (1.6% vs. 0.9%), stillbirth (0.6% vs. 0.4%), neonatal intensive care unit (NICU) admission (25% vs. 11.9%), and five-minute Apgar score < 5 (1.4% vs. 0.7%), with RRs ranging from stillbirth RR 1.6 (95% CI, 1.24-2.08) to SGA less than the third percentile RR 2.6 (95% CI, 2.4-2.82).

When the authors compared women who reported use of cannabis but *no other substances* with women who used no substances, PTB rates were higher (9.1% vs. 5.9%, RR 1.34 [1.27-1.42]) in the cannabis group. As commonly seen in other obstetrical outcomes, concomitant tobacco use, alcohol use, and opioid use drove the PTB rates higher and overshadowed cannabis use as far as impact on birth outcomes. Compared to other retrospective cohort studies assessing complex interactions between pregnancy exposures and pregnancy outcomes, this study's strength lies in a large amount of complete data (95% of included pregnancies) and more than 5,500 pregnancies with known cannabis exposure available for review. This leaves the question of confounding by other substance use less susceptible to bias.

[What effect legalization has on self-reporting is unknown, since data still lag behind state legalization.]

■ COMMENTARY

Similar to other studies evaluating cannabis use and pregnancy, the prevalence of use in pregnancy ranges from ~2-7%.[1-3] In spite of recommendations to abstain from cannabis use, women report continuing to use cannabis in pregnancy for common ailments including nausea/vomiting and anxiety.[4] Previous epidemiologic studies have summarized the risks of marijuana use in pregnancy, ranging from no overall differences in several pregnancy outcomes to increased risks of low birthweight/SGA infants, increased NICU admissions, and increased stillbirths.[5-7]

Several factors affect the ability to understand the effects of cannabis on maternal and fetal health. Assessing the use of cannabis is challenging since detection can be through self-reporting or through laboratory confirmation testing of tetrahydrocannabinol (THC) in urine or blood, neither of which is perfect. What effect legalization has on self-reporting is unknown, since data still lag behind state legalization.

Another challenge comes from limitations in existing technologies to assess THC accurately in other tissues (breast milk), which could affect the fetus/newborn directly, and which likely influences reported "effects" and risks. Finally, marijuana strains, THC concentrations, and delivery modalities (smoking, edibles, vaping, tinctures) continue to evolve and, therefore, present day cannabis is more potent than the cannabis available 5-10 (or more) years ago. Furthermore, cannabis can

be THC-heavy or cannabidiol (CBD)-heavy, or somewhere in between, and these active chemicals may have different effects on both a mother and her developing fetus.

The following are some clinical pearls to offer as the research on cannabis in pregnancy evolves:

- Screen for tobacco, alcohol, and marijuana use in pregnancy independent from a global question about "illicit drug use." Marijuana/cannabis must be asked about separately, as it is not an "illicit" drug in many states and, now, in Canada.
- Just as you do with alcohol and tobacco use in pregnancy, advise patients to stop using marijuana. The data are not clear regarding the harm or benefit.
- Recognize that women may be self-medicating mental health conditions or nausea/vomiting with marijuana. Provide safe and reasonable treatments. ■

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ABSTRACT & COMMENTARY

Molecular Analysis of Endometrial Cancer Corresponds With Outcomes in Young Women

By Melissa Moffitt, MD

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Dr. Moffitt reports no financial releationships relevant to this field of study.

SYNOPSIS: In this retrospective cohort study, researchers studied the prognosis and outcomes for young women with endometrial cancer and compared them according to tumor molecular classification.

SOURCE: Britton H, Huang L, Lum A, et al. Molecular classification defines outcomes and opportunities in young women with endometrial cancer. *Gynecol Oncol* 2019;153:487-495.

Britton et al[1] identified a cohort of 257 patients who were diagnosed with endometrial cancer before the age of 50 and for whom they had corresponding clinical and outcomes data. Half of these women were nulliparous at diagnosis, and 28% were younger than 40 years of age. Many of these patients had been categorized previously into three groups according to identified risk factors: high estrogen exposure, Lynch syndrome-like family history, or no identifiable risk.[2]

The researchers performed immunohistochemistry staining on the endometrial biopsy and/or hysterectomy specimens for p53 and for two mismatch repair (MMR) genes, PMS2 and MSH6. DNA extraction and polymerase chain reaction (PCR) testing for POLE mutations were performed. Cases were categorized first by their MMR gene status. Next, those who did not have MMR deficiency were subdivided by POLE status. Lastly, those with MMR genes intact and no POLE mutations were stratified by p53 status. Univariable survival analysis was performed for the molecularly categorized subtypes and the risk-factor categorized subtypes, including overall survival (OS), disease-specific survival (DSS), and progression-free survival (PFS). The univariable survival analysis of the molecularly categorized subtypes had many statistically significant clinical associations, including age at diagnosis, body mass index, stage, grade, histology, adjuvant treatment, and risk factor categorization.

Kaplan-Meier curves showed that molecular subtypes were associated with OS and DSS. Those with p53 mutations had the shortest OS and DSS; those with MMR deficiencies also had shorter OS and DSS. Those with POLE mutations showed the best OS and DSS, while those with intact p53 staining had outcomes nearly as good as those with POLE mutations. Multivariable survival analysis, correcting for characteristics such as age, body mass index, grade and adjuvant treatments, showed that molecular subtypes continued to be associated with OS and DSS. The risk factor subgroups were not associated with survival parameters.

■ COMMENTARY

For many years, endometrial cancer has been categorized by histology and for endometrioid carcinomas, by grade. The low-grade endometrioid adenocarcinomas that arise out of atypical endometrial hyperplasia due to excess unopposed estrogen have been termed Type 1.[3] That was to contrast them from the obviously more aggressive subtypes that arise from atrophic endometrium, without signs of excess estrogen, such as serous carcinomas, which thus were termed Type 2. This way of categorizing endometrial cancer was simple, but was not very meaningful clinically.

In 2013, The Cancer Genome Atlas[4] (TCGA) molecularly analyzed 373 endometrial cancers and found four molecular subtypes: copy number high (serous-like); copy number low (endometrioid-like); POLE (ultramutated); and micro-satellite instability (hypermutated). These subgroups were found to be associated with clinical outcomes. The technology used by TCGA is used in research currently, but cost limits its clinical use. In 2015, Talhouk et al[5] published a Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), an algorithm for pathologists to identify the four TCGA subtypes. The ProMisE algorithm is what was used by Britton et al in this study on young women.

Endometrial cancer is one of the few malignancies with increasing incidence and mortality in the United States, thought to be subsequent to the increasing rate of obesity. Although the median age of diagnosis for endometrial cancer is 63 years, more than 20% of women diagnosed with endometrial cancer are premenopausal. Young women diagnosed with endometrial cancer often seek to maintain their fertility. Only those with low-grade endometrioid adenocarcinoma, who are clinically Stage I and have imaging suggestive of minimal invasion, are appropriate candidates. Even in this optimized cohort of patients, the usual fertility-sparing treatment with progestins is effective only three-quarters of the time.[6]

In this article, the authors give us a potential tool to better assess candidates for fertility-sparing treatment: We can add molecular subtyping using the ProMisE algorithm on the endometrial sample as was done in this study. Those found to have p53 mutations and MMR deficiencies (who have worse outcomes), can be counseled to see a reproductive endocrinologist and infertility specialist for egg preservation before starting standard cancer treatments. Alternatively, patients found to have POLE mutations, or those with intact MMR and p53 expression, can be counseled regarding their expected excellent outcomes, and encouraged to pursue fertility- or ovarian-conserving therapy.

[Endometrial cancer is one of the few malignancies with increasing incidence and mortality in the United States, thought to be subsequent to the increasing rate of obesity.]

Given the growing accumulation of information correlating these TCGA subgroups to outcomes, some version of this ProMiseE algorithm will be widely adapted soon by most gynecologic pathologists and performed on routine endometrial biopsy and hysterectomy specimens. Like gynecologic oncologists, gynecologists familiar with these tests and their meaning will be grateful to know, immediately upon receipt of pathology results, how to counsel their patients more accurately on outcomes and prognosis.

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CME/CE QUESTIONS

1. **In the study by Kwan et al, the use of CT scans in pregnant women increased by how much in the U.S. sites over the study period?**
   a. 2-fold
   b. 3.7-fold
   c. 5-fold
   d. 10-fold

2. **Compared to placebo, treatment with vaginal estradiol vaginal tablet resulted in:**
   a. a significant increase in the proportion of women reporting penetrative sex in the last week.
   b. an improvement in libido and orgasm.
   c. an increase in partner satisfaction.
   d. a decrease in vaginal discharge and odor.

3. **After controlling for tobacco use and other potential confounders, the risk difference (RD) in preterm birth rates < 37 weeks was:**
   a. 2.98%.
   b. 1.75%.
   c. 0.38%.
   d. 5.88%.

4. **A 37-year-old gravida 0 (G0) is found to have a low-grade endometrioid uterine adenocarcinoma. POLE testing shows a mutation. She was hoping to achieve pregnancy in the upcoming year. She should be encouraged to:**
   a. Pursue treatment with hysterectomy ± lymphadenectomy but retain ovaries to ensure adequate treatment but maintain physiologic hormones until menopause.
   b. Pursue standard treatment with hysterectomy, BSO ± staging as the POLE mutation is meaningless.
   c. Pursue fertility-sparing therapy given expected indolent course of her disease and subsequent excellent outcomes.
   d. Pursue standard treatment with hysterectomy, BSO ± lymphadenectomy and adjuvant radiation because of expected poor outcomes.

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CME/CE OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- Explain the latest data regarding diagnosis and treatment of various diseases affecting women;
- Discuss new data concerning prenatal care, neonatal health, and complications arising in pregnancy and the perinatal period; and
- Discuss the advantages, disadvantages, and cost-effectiveness of new testing procedures in women's health.

[IN FUTURE ISSUES]

Sedentary Behavior and Urinary Incontinence