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Evidence-based commentaries on women's reproductive health

ABSTRACT & COMMENTARY

Brain Imaging and Alzheimer's Risk: Valid Surrogates or Just Pretty Pictures?

By Jeffrey T. Jensen, MD, MPH

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Dr. Jensen reports he is a consultant for and receives grant/research support from Bayer, Merck, ContraMed, and FHI360; receives grant/research support from Abbvie, HRA Pharma, Medicines 360, and CONRAD; and is a consultant for the Population Council.

SYNOPSIS: In an observational multimodality brain imaging study, investigators found sex and age differences correlated with endophenotypes of late-onset Alzheimer's disease.

SOURCE: Mosconi L, Berti V, Quinn C, et al. Sex differences in Alzheimer risk: Brain imaging of endocrine vs chronologic aging. *Neurology* 2017;89:1382-1390.

Epidemiologic studies show that Alzheimer's disease (AD) occurs more frequently in women and suggest that hormonal therapy (HT) may protect women from developing the disorder.[1] Mosconi and colleagues performed a cross-sectional, observational, multimodality brain imaging study to investigate the emergence of brain imaging patterns during the transition to menopause that might reflect AD risk. They evaluated a cohort of clinically and cognitively normal women and age-matched men between the ages of 40 to 60 years and measured "endophenotypes" (heritable, reliable, and quantifiable biological traits more closely related to the root cause of the disease than the broad clinical phenotype) considered reflective of late-onset AD risk.

To justify the neuroimaging used, the authors cited literature that links declining levels of estrogen during perimenopause to altered glucose metabolism that in turn induces a hypometabolic state accompanied by increased fatty acid catabolism. This leads to β-amyloid (a hallmark of AD pathology) deposition and the decline in synaptic plasticity associated with the development of AD later in life.[2] To test whether

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age- and sex hormone-related effects influence the risk of AD development, they evaluated subjects using multimodality brain imaging measuring three putative biomarkers associated with AD development: 1) β-amyloid deposition (C^{11}–Pittsburgh compound B [PiB]) PET scan); 2) glucose hypometabolism (F^{18}-fluoro-2-deoxyglucose [FDG]) PET scan; and 3) brain atrophy (MRI). These have been proposed as surrogate measures of AD risk.[3]

The authors selected subjects for this study from a larger pool of clinically and cognitively normal adults participating in brain imaging studies for AD.[4] After exclusion, they selected 42 women and used clinical judgment and symptoms to group them as: asymptomatic perimenopausal women (control, n = 15); symptomatic perimenopausal women (PERI, n = 13); and postmenopausal women (POST, n = 14). They also selected a cohort of 18 age- and education-matched men. All of the subjects previously had received volumetric MRI, PiB, and FDG-PET scans using the same standardized procedures. All subjects underwent genotyping for APOE4, a genetic marker for brain atrophy.

With the exception of age (older in the POST group), the female groups were comparable on clinical and neuropsychological measures and APOE4 distribution. Compared to asymptomatic perimenopausal control women (and to men) and controlling for age, the PERI and POST groups exhibited significantly increased indicators of AD endophenotype, including hypometabolism, increased β-amyloid deposition, and reduced gray and white matter volumes in AD-vulnerable regions. These AD biomarker abnormalities were greatest in POST, intermediate in PERI, and lowest in control women ($P < 0.001$). β-amyloid deposition was significantly greater in APOE4-positive POST women compared to the other groups.

Based on these multimodality brain imaging results demonstrating sex differences in the development of the AD endophenotype, the authors concluded that the preclinical AD phase begins early in the female aging process during the endocrine transition of perimenopause. They suggested that therapeutic intervention with estrogen during the perimenopause might reduce the risk of AD development.

■ COMMENTARY

A catchy image on my electronic edition of *The New York Times*, The Menopause-Alzheimer's Connection,[5] drew my attention to this manuscript. In the *Times* article, the lead author, a neuroscientist named Dr. Lisa Mosconi, presents a lay summary of her recent publication. The article begins with the impressive image, a PET scan, of an AD sufferer's brain in full color showing serial sections highlighted with electric red, green, blue, and magenta. You don't need to be a neuroradiologist to be impressed by this image. It looks important and not the way you would like to see your brain. Dr. Mosconi leads off the article dramatically stating, "In the next three minutes, three people will develop Alzheimer's disease. Two of them will be women." A clear call for action.

She goes on to explain that the estrogen deficiency that develops with the transition to menopause explains this gender difference in AD risk. She summarizes the research results from her group as evidence proving this association. The concluding recommendation is to initiate hormonal therapy (HT) early to prevent cognitive decline. This recommendation also falls in line with the literature supporting the "timing" hypothesis to maximize benefits of HT for cardiovascular disease.[6]

While I want to believe in this mechanism, I need to point out that this paper greatly overstates the significance of the data. We need to be intellectually honest about the science, and not cherry-pick results consistent with our beliefs. Major limitations of the multimodality brain imaging study include classification and ascertainment bias. They authors used history to classify women into healthy control, perimenopausal, and menopausal groups. There is no mention of hormonal therapy or whether this was exclusionary. They also do not report hormonal contraception use. Since the assessment of the multimodality brain imaging is somewhat subjective, it would be important to know whether the authors used a blinded independent reader. Unfortunately, the authors fail to mention this important detail. While the data support an age-associated adverse change in AD imaging findings in women, they do not provide convincing evidence that this is due to hypoestrogenism. Although they state that no age-related changes were observed in the

smaller cohort of age-matched men, they do not present sufficient data to determine if this is true. They present no ad hoc hypothesized effect size, and no justification for the sample size selected. Furthermore, the use of imaging as a surrogate for Alzheimer risk has not been validated.

What do we know about cognition and hormonal therapy? In the subset of women aged 65 years or older in the Women's Health Initiative (WHI) study, HT did not improve cognitive function when compared with placebo, and more women in the HT group experienced cognitive decline.[7] Just as with cardiovascular disease, one explanation for the negative effects observed in WHI and the positive benefits seen in observational studies may be a critical window for initiation of treatment.

The randomized ELITE-Cog study was designed to evaluate this "aging" or "timing" hypothesis with respect to cognitive outcomes.[8] The primary hypothesis of this study was that postmenopausal estrogen initiated soon after menopause (< 6 years) would affect verbal memory differently than initiation at a later time (≥ 10 years). Subjects were randomized to receive oral 17β-estradiol (1 mg daily) or matching placebo. Women with a uterus received cyclic micronized progesterone as a 4% vaginal gel or matched placebo gel for 10 days each month. The investigators assessed cognitive skills at baseline, 2.5 years, and five years using a comprehensive neuropsychological battery that emphasized standardized tests sensitive to age-related changes. Results of the cognitive tests showed no overall significant or clinically important difference in verbal memory in women who received estradiol compared to placebo, and no difference with respect to early or late initiation of hormonal therapy. A similar lack of effect was seen for executive function and global cognition. The authors concluded that estradiol therapy neither benefits nor harms cognitive ability regardless of time of initiation of HT after menopause.

The results of ELITE-Cog were consistent with KEEPS-Cog.[9] The KEEPS-Cog study randomized recently postmenopausal women to receive transdermal estradiol or oral conjugated equine estrogens (with cyclic micronized progesterone in women with a uterus). Participants averaged 53 years of age and were 1.4 years past their last menstrual period. As with ELITE-Cog, no treatment-related benefit of HT was seen with respect to cognitive function.

While the KEEPS-Cog, ELITE-Cog, and WHI results do not support the use of estrogen therapy to prevent cognitive decline in postmenopausal women, all of these studies have limitations. Some brain researchers (like Mosconi) believe that susceptibility for irreversible cognitive effects may manifest in the perimenopausal transition.[10] It also could be that the estrogen doses studied have been too low. The median estradiol level on treatment in the ELITE-Cog study was around 40 pg/mL. KEEPS-Cog used a very low dose of conjugated equine estrogens. These may be insufficient to produce cardiovascular or brain benefits.

[While I want to believe in this mechanism, I need to point out that this paper greatly overstates the significance of the data. We need to be intellectually honest and not cherry-pick results consistent with our beliefs.]

While the results of Mosconi et al do not definitively support a role of HT in the prevention of Alzheimer's disease, these brain imaging techniques need further evaluation. I would like to see a true prospective multimodality brain imaging study similar to ELITE-Cog randomizing women early and late in the menopausal transition to HT or placebo. This powerful tool could help provide real evidence in support of a cognitive benefit of HT. Right now, all we have is pretty pictures. ■

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ABSTRACT & COMMENTARY

Fertility Preservation in Women With Borderline Ovarian Tumors

By Robert W. Rebar, MD

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Dr. Rebar reports he is the chair of the data and safety monitoring board for Myovant Sciences.

SYNOPSIS: A large retrospective cohort analysis from a single medical center suggests that fertility preservation in women with borderline ovarian tumors does not decrease length of survival.

SOURCE: Helpman L, Yaniv A, Beiner ME, et al. Fertility preservation in women with borderline ovarian tumors — how does it impact disease outcome? A cohort study. *Acta Obstet Gynecol Scand* 2017:96:1300-1306.

Borderline ovarian tumors (BOT), sometimes termed ovarian tumors of low malignant potential, account for the minority of all epithelial ovarian tumors but are diagnosed much more commonly in women of reproductive age than invasive cancers. This prompted investigators at one medical center to assess the effect of fertility-preserving surgery on disease outcomes, including recurrence and survival.

A historical cohort of 213 sequential women with BOT were identified with sufficient data for analysis from a prospectively maintained database between the years 1981 and 2011. Mean follow-up for the cohort was 75 months, with a total follow-up period of 1,331 person-years. The mean age in the cohort was 38.7 years, with 132 (62%) being ≤ 40 years of age. A total of 112 (85%) of the younger women (age ≤ 40 years) and 124 women in all had fertility-preserving surgery, with such surgery defined as surgery sparing the uterus and some ovarian tissue to allow spontaneous conception in the future. There were 67 pregnancies in 42 of the 112 women (38%) younger than 40 years of age who had fertility-preserving surgery, with more than one pregnancy documented in 22 women. In all, 50 patients (24%) developed recurrences, with 40 of those having had fertility-sparing surgery. Recurrence was localized in 37 patients and disseminated (usually peritoneal) in 11 cases. Twenty patients (9%) died over the course of follow-up, with 11 succumbing to their disease but nine dying from other causes (and no evidence of recurrence). Six of those 11 cases (55%) had fertility-preserving surgery. Of note is the fact that eight of those dying of their disease had evidence of capsule rupture, tumor on the ovarian surface, or malignant cells in the ascites fluid or peritoneal washings (stage 1C) at the time of staging surgery. On multivariate analysis, fertility preservation (hazard ratio [HR], 2.57; 95% confidence interval [CI], 1.1-6; $P = 0.029$) and advanced stage of 1C or greater (HR, 4.15; 95% CI, 2.3-7.6; $P < 0.001$) were associated independently with recurrence on multivariate analysis. Fertility preservation was associated with shorter disease-free survival (mean of 177 months for women having fertility-sparing surgery and of 235 months for those who did; $P < 0.001$). However, both fertility preservation and ovarian conservation were not associated with overall survival by either log-rank test or the Kaplan-Meier method for stage 1 disease.

■ COMMENTARY

The findings of this study become more relevant as women delay childbearing until later in life. Although retrospective and from a single institution, the results are reassuring. It is unlikely that a large, sufficiently powered, randomized trial of fertility-sparing surgery for early-stage BOT ever will be conducted. Although the risk of mortality with fertility-sparing appears low, it also appears that the risk of recurrence is increased. Thus, patients with BOT contemplating fertility preservation must be counseled carefully to pursue childbearing as soon as possible. There are no guarantees that the disease will not recur and lead to death.

It is important to note that many findings in this study are consistent with prior reports. The low mortality of < 5% is comparable to another European study.[1] The fact that fertility-sparing surgery had little effect on survival is consistent with prior studies[2-5] and is generally attributed to the potential for further surgery to cure any recurrences. A relatively recent systematic review of fertility preservation in BOT concluded that the risk of recurrence for conservatively managed early disease is 13%, with the risk rising to 38% in advanced disease.[5] In this study, consistent with the previously mentioned studies, univariate analysis found an association between recurrence and a number of other factors, including disease stage and peritoneal spread, CA 125 levels, and serous histology. A pooled estimate for spontaneous pregnancy after conservative surgery for BOT was 54% (95% CI, 38-70%),[5] with more pregnancies occurring in women with non-serous (mainly mucinous) neoplasms.[6] Few women in this study received adjuvant chemotherapy, but those who

did had an increased risk of dying, consistent with a Cochrane review[7] not supporting its use. These data are consistent with a recent review noting the risk of progression to invasive BOT was only 2-3%.[8]

There is one small randomized trial published in 2007 and updated in 2010 that assists us in counseling women who desire a future pregnancy.[9,10] Thirty-two patients with bilateral BOT were treated laparoscopically and randomized to bilateral cystectomy vs. unilateral salpingo-oophorectomy on the side with the larger lesion and contralateral cystectomy. Follow-up at 81 months revealed no differences in the cumulative rates of recurrence. However, the cumulative pregnancy rate and the cumulative rate of a first pregnancy were higher with bilateral cystectomy.[9] Those women with bilateral cystectomy had a shorter time to first recurrence and a higher rate of radical treatment of the recurrence.[10] These data can be interpreted as suggesting that bilateral cystectomy should be performed for bilateral disease if technically feasible for fertility preservation. Extrapolating this further suggests that unilateral cystectomy should be preferred over unilateral salpingo-oophorectomy for unilateral disease in women desiring future children. Although biopsy of a contralateral normal-appearing ovary is suggested by some, the yield is low and the risk of causing adhesions decreasing fertility is real.[5]

This study does not tell us about the effect of assisted reproduction in women with BOT. This too has significance, as more women delay childbearing and seek assistance for relative infertility. Preservation of the uterus if both ovaries are removed allows for future assisted reproduction.[11,12] In vitro fertilization has been reported only in case reports and small series.[5] As a consequence, little is known about the effects of fertility drugs after conservative treatment of BOT but it has been used after appropriate counseling. Because freezing ovarian tissue that appears grossly normal may contain and subsequently introduce malignant cells with re-transplantation, this approach to infertility would appear to be contraindicated at least at present. ■

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ABSTRACT & COMMENTARY

Is Vaginal Estrogen Still the Gold Standard for Treating GSM?

By Rebecca H. Allen, MD, MPH

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Dr. Allen reports she is a Nexplanon trainer for Merck.

SYNOPSIS: In this 12-week randomized, controlled trial of 302 women, neither vaginal estrogen nor vaginal moisturizer was more effective than placebo for reducing the participants' most bothersome symptom (pain with vaginal penetration, vulvovaginal itching, vulvovaginal pain, vaginal dryness, or vulvovaginal irritation).

SOURCE: Mitchell CM, Reed SD, Diem S, et al. Efficacy of vaginal estradiol or vaginal moisturizer vs. placebo for treating postmenopausal vulvovaginal symptoms: A randomized controlled trial. *JAMA Intern Med* 2018; March 19. doi: 10.1001/jamainternmed.2018.0116.

This was a randomized, double-blind, placebo-controlled, 12-week trial to assess treatments for genitourinary syndrome of menopause (GSM). Inclusion criteria were women age 45 to 70 years who were at least two years since last menses with at least one moderate to severe symptom of vulvovaginal itching, pain, irritation, or dryness experienced at least weekly in the past 30 days or pain with vaginal penetration at least once monthly. Exclusion criteria were current vaginal infection, use of hormonal medication in the past two months, use of antibiotics or vaginal moisturizer in the past month, or chronic premenopausal vulvovaginal symptoms. Women were randomized 1:1:1 to Vagifem 10 mcg tablet + placebo vaginal gel, placebo vaginal tablet + over-the-counter Replens vaginal moisturizer, or placebo tablet + placebo gel. Vaginal tablets were to be used daily for two weeks and then twice a week for the remaining 10 weeks and the vaginal moisturizer/placebo gel was used every three days throughout the trial. The placebo gel was similar to KY Jelly. The primary outcome was the severity of the most bothersome symptom (MBS) defined by the subject at enrollment (vulvovaginal itching, pain, irritation, dryness, or pain with vaginal penetration) rated from 0 to 3 (none, mild, moderate, severe). Secondary outcomes included the vaginal symptom index (mean severity score of the five vulvovaginal symptoms listed as MBS choices), Female Sexual Function Index, vaginal maturation index, and vaginal pH. Outcomes were assessed at four and 12 weeks.

A total of 302 women were randomized and only 3% were lost to follow-up. The mean age of the sample was 61 years and the majority were white (≥ 85%), married (≥ 81%), and sexually active (67% male partner, 1% female partners, 32% self-stimulation only). Participants reported the following MBS: pain with vaginal penetration (60%), vaginal dryness (21%), itching (7%), irritation (6%), and pain (5%). Vaginal estradiol tablet + placebo gel compared to placebo tablet + placebo gel reduced MBS severity by similar degrees (-1.4 vs. -1.3; $P = 0.25$). Vaginal moisturizer + placebo tablet compared to dual placebo also reduced MBS severity by similar amounts (-1.2 vs. -1.3; $P = 0.31$). Vaginal estradiol showed expected improvements in vaginal pH and increased the vaginal maturation index compared to placebo (46% vs. 12%; $P < 0.001$ and 57% vs. 11%; $P < 0.001$, respectively). The vaginal moisturizer did not affect these indices. There was no difference between the three groups on the Female Sexual Function Index. Although treatment satisfaction was similar between the three groups, more women in the estradiol tablet arm reported a "meaningful benefit" from treatment than the placebo group (80% vs. 65%; $P = 0.02$), but no difference was seen between the moisturizer and placebo groups (57% vs. 65%; $P = 0.39$).

■ COMMENTARY

Many postmenopausal women report symptoms related to vulvovaginal atrophy such as vaginal dryness (70%) and dyspareunia (40%).[1] With the decline of estrogen in the menopausal period, the vulvovaginal tissue becomes thinner, the vagina becomes more alkaline, and vaginal secretions can decrease.[2] The North American Menopause Society (NAMS) has termed this the GSM. Treatment recommendations include vaginal lubricants, vaginal moisturizers, and local vaginal estrogen if systemic estrogen therapy is not needed or desired. Vaginal moisturizers are supposed to have components that adhere to the vagina, allowing intermittent dosing, whereas vaginal lubricants typically are used prior to intercourse. Vaginal estrogen treatments include 10 mcg estradiol tablets, a three-month estradiol vaginal ring that releases 7.5 mcg daily, and estradiol or conjugated estrogen cream.[2]

The authors of this study decided to evaluate the efficacy of vaginal estradiol tablets and vaginal moisturizer, comparing each to a placebo. They felt that many women avoided products containing estrogen because of concerns about safety, so they wanted to assess a low-dose estrogen product and a moisturizer product. The results were surprising given that vaginal estradiol tablets did no better than placebo or vaginal moisturizer (although it was not technically a head-to-head trial) in terms of participant symptoms. Vaginal estradiol tablets were more effective in improving objective markers of vaginal health showing their biologic action. A previous Cochrane Review concluded that vaginal estrogen in various forms was superior to placebo, although the quality of the evidence was low, mostly because of small sample sizes.[3] In addition, a recent systematic review of the evidence by the Society of Gynecologic Surgeons also concluded that "all commercially available vaginal estrogens effectively relieve common vulvovaginal atrophy-related complaints."[4] The fact that the vaginal moisturizer did no better than placebo gel is not as surprising, since the placebo gel was similar to KY Jelly, containing hydroxyethylcellulose and having a similar viscosity.

An accompanying editorial by two internists concluded that women should just choose the cheapest over-the-counter lubricant available to treat vulvovaginal symptoms rather than visiting their physician for a vaginal estrogen prescription.[5] This conclusion seems extreme as there certainly are limitations to this study. The follow-up was short-term (12 weeks) and the use of the placebo gel likely contributed to the large placebo response. In addition, 10 mcg of estradiol may be too low of a dose to treat dyspareunia and other bothersome symptoms in some women. The response of NAMS to this study was to state that a "single short-term and underpowered clinical trial does not override a large body of previous evidence."[6] I agree with that statement and likely will not change my practice based on this study. NAMS already currently recommends vaginal lubricants and moisturizers as first-line treatment for GSM. If a woman fails those treatments, then a trial of vaginal estrogen makes clinical and biologic sense. ■

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ABSTRACT & COMMENTARY

The Risk of Malignancy in Hysterectomy

By Molly A. Brewer, DVM, MD, MS

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

SYNOPSIS: There has been significant publicity about the risk of malignancy associated with morcellation in hysterectomy, but in reality the incidence is quite low.

SOURCE: Desai VB, Wright JD, Schwartz PE, et al. Occult gynecologic cancer in women undergoing hysterectomy or myomectomy for benign indications. *Obstet Gynecol* 2018;131:642-651.

Over the last several years, there has been increasing concern about the risk of an occult malignancy at the time of hysterectomy or myomectomy. There remains a risk of cervical, endometrial, or myometrial malignancy even when an adequate workup has been done. In addition, there have been many reports in the literature of occult fallopian tube and ovarian cancer in the BRCA+ population at the time of prophylactic bilateral salpingo-oophorectomy, ranging from 2-12% depending on the study. However, the risks had not been at the forefront until a physician in Boston had a laparoscopic hysterectomy with power morcellation and was found to have a leiomyosarcoma. When she recurred, she and her physician husband blamed the power morcellation for her recurrence, subsequent progression, and, ultimately, her death. Prior to her decline, she and her husband became active politically against the use of the power morcellator, stating it was an instrument of harm since its use potentially upstaged an occult cancer. The end-result was that this important laparoscopic tool was removed from the gynecologic surgery tool box, and surgeons were left with the quandary of how to remove tissue through small incisions. Despite significant data suggesting that leiomyosarcomas are rare cancers with poor ability to diagnose preoperatively and that the risk of malignancy is less than the risk for converting to an open procedure, hospital after hospital removed power morcellators from their shelves.

Desai et al analyzed the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP), which is a voluntary reporting program with de-identified patient information. The database contains appropriate clinical information, including age, comorbidities, body mass index (BMI), pelvic inflammatory disease, prior surgeries, endometriosis, uterine weight, and surgical approach, but preoperative workup information is not available. According to ACS NSQIP, women who had hysterectomies for benign indications had a 1.44% risk of uterine cancer, 0.6% risk of cervical cancer, and 0.19% risk of ovarian cancer in their final pathology. The surgical approach influenced the risk, with a slightly higher risk in laparoscopic procedures and slightly lower risk in vaginal or supracervical hysterectomies. Women having myomectomy were younger and had a lower risk of malignancy, with a 0.21% risk of a uterine malignancy. Age was an important risk factor for malignancy, with women 55 years of age and older having a 9.72% risk of uterine cancer, compared to 1.06% in women younger than 55 years of age. Age of 55 years or older also was associated with an increased risk of both cervical and ovarian cancer. Given that the risk of malignancy increases with age, these results are not surprising.

In a prior article, Wright et al quoted a 0.19% risk of uterine cancer in women who did not undergo morcellation and 0.09% in women who did have morcellation. The risk of malignancy again was increased with age.[1] In 2018, Yuk et all found hysteroscopy was associated with an even greater incidence of unexpected uterine malignancy, with a 0.86% risk with hysteroscopic myomectomy and 1.11% risk with polypectomy.[2] These findings are not surprising because patients would have had a specific indication for the surgery, primarily abnormal bleeding,

which has a higher risk of malignancy. Another large, single-institution study found occult malignancy in 0.19% of hysterectomies done for benign indications.[3] Those premenopausal patients with an unexpected endometrial malignancy all had a BMI in the obese to morbidly obese range, which increased their risk of endometrial pathology. In 2016, Wise et al found that 5% of their patients younger than 45 years of age who presented with abnormal uterine bleeding had complex hyperplasia or cancer, and patients with a BMI ≥ 30 kg/m^2 had a four-fold increased risk of endometrial pathology, suggesting that risk of malignancy is increased in young obese women.[4] They concluded that BMI rather than age should be the criterion for endometrial sampling prior to hysterectomy.

■ COMMENTARY

Although there has been significant publicity about the risk of malignancy associated with morcellation, the reality is that the incidence is quite low (< 1% of an occult cancer at time of surgery). Older age and high BMI are both risk factors for occult malignancy. Endometrial biopsies prior to surgery will reduce the risk of an unexpected malignancy and aid in diagnosis most of the time. However, patients should be counseled that there is still a risk of malignancy when undergoing hysterectomy for benign indications, especially in older women with insufficient tissue on endometrial biopsy. However, given the very low risk of malignancy in carefully screened patients, the uproar and negative public opinion against power morcellation seems to have been blown out of proportion and was driven by politics rather than data. ■

REFERENCES

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CME/CE QUESTIONS

1. **Multimodality brain imaging studies demonstrated that patterns suggestive of Alzheimer's disease risk:**
   a. occur more commonly in postmenopausal women than premenopausal women.
   b. do not develop with administration of conjugated equine estrogens.
   c. never occur in women with body mass index > 35 kg/m^2 and hearing loss.
   d. decrease conversational fluency only in women with college degrees.
2. **Conservative fertility-sparing surgery does not increase the chances of survival for women with early stage borderline ovarian tumors.**
   a. True
   b. False
3. **In the study by Mitchell et al, vaginal estradiol tablets improved which of the following compared to placebo?**
   a. Satisfaction with treatment
   b. Vaginal maturation index
   c. Pain with vaginal penetration
   d. Vaginal dryness
4. **The risk of malignancy is lowest in which of the following groups of women?**
   a. Obese women
   b. Women ≥ 55 years of age
   c. Both obese women and women ≥ 55 years of age
   d. Neither obese women or women ≥ 55 years of age

[IN FUTURE ISSUES]

Management of Intrauterine Growth Restriction: Revisited

Does Childhood Adversity Affect the Menopausal Transition?