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Moving Beyond Reflexive and Prophylactic Gynecologic Surgery

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Although recent data have documented the declining rate of hysterectomy, hysterectomy with and without concomitant oophorectomy and salpingectomy remains the second most common surgical procedure for women in the United States.[1,2] Because the cumulative incidence of hysterectomy approaches 50% in the United States, and less than 10% of hysterectomies are performed for any type of cancer or precancer, any long-term sequelae of hysterectomy have profound societal implications.[3,4] These sequelae are further magnified because oophorectomy and salpingectomy are often performed without pathologic diagnoses but, instead, with the intent to prevent ovarian cancer.

A substantial body of work now details the sequelae of hysterectomy over up to 20 years of follow-up for all nonmalignant indications.[5–10] Moreover; because the mean age of women undergoing hysterectomy with ovarian conservation is approximately 44 years for indications such as uterine fibroids, adenomyosis, and endometriosis, additional sequelae will accumulate as these cohorts age to menopause and beyond, when the risk of adverse health outcomes in the general population is highest.[1]

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Gynecologists historically were taught to remove the ovaries prophylactically in the majority of women undergoing hysterectomy. The stated rationale for oophorectomy was the prevention of ovarian cancer, but an additional unstated assumption was that the ovaries had little physiological relevance beyond procreation. However, data regarding the impact of early natural menopause are building, with a recent pooled analysis of more than 300,000 women confirming a stepwise increase in risk of cardiovascular disease with decreasing age of natural menopause.[11]

Data from the Mayo Clinic Cohort Study of Oophorectomy and Aging (MOA), starting in 2006, and the Nurse's Health Study, starting in 2009, appropriately focused the medical community on the risks of hysterectomy with bilateral salpingooophorectomy (BSO) compared with no surgery or with hysterectomy with ovarian conservation.[5,6] In the MOA study, women undergoing bilateral oophorectomy before age 45 years had a significantly greater risk of all-cause mortality over nearly 30 years of follow-up (hazard ratio [HR], 1.67; 95% confidence interval [CI], 1.16 to 2.40) compared with population-based referent women without surgery.[5] Similarly, the Nurses' Health Study showed a 12% higher risk of mortality over 24 years with hysterectomy with BSO compared with women undergoing hysterectomy with ovarian conservation, leading to the estimate of 1 additional death for every 9 oophorectomies (number needed to harm).[6]

The Mayo Clinic investigators replicated their initial findings in a new cohort: MOA-2. Further research in MOA-2 demonstrated that BSO is linked to a variety of chronic conditions that can be combined into the concept of multimorbidity of aging, as defined by the Department of Health and Human Services.[8] Multimorbidity has been used as a clinical marker of accelerated aging and encompasses 5 mental health conditions, 7 cardiometabolic conditions, and 6 other somatic diseases including arthritis, asthma, and chronic obstructive pulmonary disease.[8] The MOA-2 study showed an increase in *de novo* rates of 8 of these 18 conditions and a 22% greater risk of accumulated multimorbidity in women undergoing BSO before age 46 compared with referent women who retain both ovaries. The risk was further increased with younger age of women at the time of oophorectomy.[8]

Newer studies have shown that there are also substantial long-term health risks following hysterectomy with conservation of both ovaries, beyond factors affecting the quality of life, such as vaginal prolapse, earlier menopause, and weight gain. These recent studies showed a substantially greater risk of *de novo* cardiovascular morbidity and mood disorders.[9,10] Compared with women without surgery, women undergoing hysterectomy with bilateral ovarian conservation had a higher risk of *de novo* hypertension (13% more), hyperlipidemia (14% more), cardiac arrhythmias (17% more), obesity (18% more), and coronary artery disease (33% more) that remained significant even after adjustment for 20 pre-existing chronic conditions and other potential confounders.[9] Risks of *de novo* depression (HR, 1.26; 95% CI, 1.12 to 1.41) and anxiety (HR, 1.22; 95% CI, 1.08 to 1.38) were also increased following isolated hysterectomy.[10] For most of these *de novo* morbid outcomes, risks were greatest for women who underwent hysterectomy younger than age 35.[9]

Moreover, the initial MOA study showed that loss of even 1 ovary in a premenopausal woman (unilateral oophorectomy) is associated with a 46% greater risk of cognitive

impairment or dementia late in life, independent of potential confounders. Therefore, gynecologic surgeries have profound long-term risks.[7] Historically, unilateral oophorectomy was considered safe and free of sequelae. Focusing only on improvements of short-term outcomes, without articulating and quantifying the long-term issues, is equivalent to focusing on the trees rather than the forest.

Indications for hysterectomy with and without ovarian conservation vary among women, and this variation is associated with factors that also increase the risk of sequelae of cardiovascular and mental health, for example. However, the likelihood of a clinician recommending hysterectomy “to cure” endometriosis or uterine fibroids with or without ovarian conservation—and the likelihood a woman will accept the surgery—demonstrably varies by geographic, economic, and other sociologic indicators. Women undergoing hysterectomy tend to have lower levels of education, lower rates of health insurance, poorer physical and mental health, and are more likely to live in regions without easy access to tertiary care.[12] In addition, women undergoing hysterectomy appear to be significantly more likely to have experienced adverse childhood or adult events including abuse and trauma.[13] These contributing factors may be a part of the etiology of the downstream medical morbidities of hysterectomy, and thus it is critical to prioritize alternatives to hysterectomy —especially for these high-risk women—when appropriate.

Despite this evidence, there have been calls to expand the role of prophylactic oophorectomy and/or salpingectomy.[14–17] For example, there is a 2% higher risk of ovarian cancer among women with endometriosis. This 2% increased risk for women with endometriosis is still within the range of population estimates of 1% to 3% lifetime ovarian cancer risk and represents a small proportion of the lifetime risk of ovarian cancer of 39% with BRCA1 and 11–17% with BRCA2 pathogenic variants.[18] Nonetheless, many women with endometriosis are counseled to consider BSO for the prevention of ovarian cancer when they have completed childbearing.

Similarly, there has been a call within the gynecologic community for “opportunistic salpingectomy;” removal of both fallopian tubes at the time of hysterectomy. The rationale for prophylactic salpingectomy is convincing evidence that some cancers that were previously thought to be ovarian arise from the fallopian tube. The American College of Obstetricians and Gynecologists recently called for opportunistic salpingectomy to prevent ovarian cancer both in high-risk women (those with BRCA1 and BRACA2 high-risk variants) and those at population risk of ovarian cancer.[16] However, a recent meta-analysis showed no studies confirming the decreased risk of cancer after this procedure, insufficient data to assess if surgical outcomes were different with and without salpingectomy, and data on preservation of ovarian reserve for only 6 months following surgery; a follow-up duration deemed inadequate for many younger women undergoing this surgery.[19]

In stark contrast, there is indisputable evidence that 11.6% of men will be diagnosed with prostate cancer in their lifetime—approximately 5 times a woman’s lifetime risk of ovarian cancer (1% to 3%)—and it will cause the death of 9% of men aged 55 to 64 and one-third of men aged 75 and older, representing the second leading cause of death for men in the United States.[20] Genetic variants contribute to 90% of advanced prostate cancer cases, including

14% of cases carrying a variant in the BRCA1 or BRCA2 gene.[21] Although the parallels are not precise between the 2 diseases, there has been no call for prophylactic prostatectomy for high-risk men by any medical society, despite emerging data that suggest positive short-term outcomes for prophylactic laparoscopic radical prostatectomy—including improved urinary function and quality of life— with high likelihood of normal erectile function.[22] In further contrast to the approach and rhetoric for women's health, even among men with documented prostate cancer, the focus has shifted toward protecting men from over-intervention for less aggressive prostate cancer subtypes.

CONCLUSION

We strongly advocate using evidence to guide gynecologic surgery. We are now seeing the unintended consequences of assuming that the uterus and ovaries are only reproductive organs. Although women with high risk of future disease—such as those with BRCA1 and BRACA2 genetic variants—require prophylactic surgery, extending this practice to women at average risk of ovarian and fallopian tube cancer is not evidence based and exposes women not only to the risks of surgery but potentially also to increased long-term risk of somatic and mental diseases for which the average risk is already much higher than that of ovarian cancer.[18]

The trend in medicine is clearly away from surgery. For breast cancer, we have evolved from the 19th-century model of radical surgery to the 21st-century view of minimal surgery for diagnosis and control of local disease. Similarly, with prostate cancer, surgery is being replaced by multiple modalities of less invasive interventional therapy and medications, including more precise disease stratification, tying disease aggression with treatment invasiveness. Let's move forward in 21st-century gynecology to a "less-is-more" and "surgery-only-as-indicated" paradigm, as with other diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

BSO	bilateral salpingoophorectomy
CI	confidence interval
HR	hazard ratio
MOA	Mayo Clinic Cohort Study of Oophorectomy and Aging

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