

Parker WH, Broder MS, Liu Z, Shoupe D, Farquhar C, Berek JS. Ovarian conservation at the time of hysterectomy for benign disease. *Obstet Gynecol.* 2005;106:219-226.

**David S. Guzick, MD, PhD**  
Professor of ObGyn and Dean,  
School of Medicine and Dentistry,  
University of Rochester,  
Rochester, NY

**Andrew W. Menzin, MD**  
Associate Chief of Gyn Oncology  
and Residency Program Director,  
Department of ObGyn, North Shore  
University Hospital, Manhasset, NY,  
and Clinical Associate Professor  
of ObGyn, New York University  
School of Medicine, New York City

### FAST TRACK

**About half of all women over 40 will die of heart disease, while fewer than 1% will die of ovarian cancer**

## Q Is it better to remove or spare ovaries at hysterectomy?

**A** This question should be decided case by case despite new findings concluding that ovarian conservation until the age of 65 improves survival among women with benign disease.

It only *seems* that this controversy is coming to the fore for the first time. In reality, it has been hotly debated for decades. One camp favors oophorectomy to prevent ovarian cancer; the other, preservation of the ovaries to reduce the risk of heart disease and hip fracture.

### ■ What is the function of the postovulatory ovary?

**GUZICK:** Some experts recommend conserving the ovaries to reduce the risk of heart disease. Why? The postovulatory ovary continues to produce androgens, which are converted to circulating estrogens. The androgens themselves are said to improve libido (itself a controversial assertion),<sup>1</sup> and their conversion to estrogens may reduce the risk of heart disease<sup>2</sup> and hip fracture.<sup>3</sup>

Parker and colleagues used a Markov decision-analysis model to estimate whether, on balance, the ovaries should be removed or conserved during hysterectomy for benign disease in women at least 40 years old. Using this model, ovarian conservation averted enough heart disease and hip fracture cases to more than offset new cases of ovarian and breast cancers.

About half of all women older than 40 will die of heart disease,<sup>4</sup> while fewer than 1% will die of ovarian cancer.<sup>5</sup> If women

undergoing hysterectomy for benign disease are roughly 50 times more likely to die of heart disease than ovarian cancer, then clearly even a small protective effect of ovarian conservation on heart disease will outweigh the potential for ovarian cancer.

For the moment, let's take the study by Parker and colleagues at face value. Given the high base rate of cardiovascular disease, it is not surprising that oophorectomy markedly diminishes the overall probability of survival at age 80 among women undergoing hysterectomy at age 50 to 54. The authors estimate that oophorectomy reduces this probability from 62% to 54%. Moreover, the estimated impact of oophorectomy on mortality varies by age. This effect is built into the model because of the age-associated increase in the base rate of ovarian cancer mortality and the estimate that the risk of coronary heart disease declines 6% each year oophorectomy is delayed after menopause.<sup>6</sup>

Significant differences in survival curves between groups of women undergoing ovarian removal or conservation are found between the ages of 40 and 54, and the curves converge after age 65. Thus, Parker and colleagues conclude that "ovarian conservation until age 65 benefits long-term survival."

### Other factors may influence survival

**GUZICK:** Ovarian conservation reduces hip fracture<sup>3</sup> but increases breast cancer, at least up until age 50.<sup>6</sup> Such factors are included in the Parker analysis, but the main drivers of the model are heart disease

and ovarian cancer. The conceptual framework for the model, and the pattern of the results, are clear strengths of this study.

**MENZIN:** Parker et al noted that their study did not address the benefits of oophorectomy among women with known or possible hereditary predisposition to ovarian cancer. Nevertheless, being aware of this major risk factor and its relevance to an informed consent discussion of hysterectomy is important, especially given the recognized benefits of risk-reducing surgery in this setting.

For women whose risk of ovarian cancer is equivalent to that of the general population, the decision is more complex. Hysterectomy, even with ovarian conservation, itself appears to reduce the risk of ovarian cancer by 10% to 40%—probably because abnormal-appearing ovaries are usually removed at hysterectomy.<sup>7,8</sup> The prognosis of ovarian cancer in conserved ovaries appears equivalent to that in women without hysterectomy,<sup>9</sup> although several studies suggest that 5% to 15% of ovarian cancers might have been prevented by oophorectomy at the time of prior hysterectomy for benign disease.

## ■ Why the Parker findings can't be taken at face value

**GUZICK:** The estimated benefit of ovarian conservation in regard to heart disease was based on data acquired between 1976 and 1982 from the Nurses' Health Study (NHS).<sup>2</sup> This is problematic for several reasons. First, the relative risk of 2.2 was estimated in the NHS for coronary heart disease *events*, not deaths.<sup>2</sup> It is not clear how Parker et al converted relative risk of events to relative risk of deaths, but apparently the risk estimate for events was applied to a baseline death rate. If so, then, because not all women with a cardiovascular event from 1976 to 1982 died of cardiovascular disease, the effect of oophorectomy is overstated.

Translating event effects to mortality effects is even more problematic when applied to contemporary medical practice.

Women at risk of common cardiovascular problems such as hypertension and coronary artery disease now have the benefit of advances in diagnosis (blood pressure monitoring, biochemical markers, endothelial function tests, and coronary imaging) and treatment (eg, statins, antihypertensives, and coronary artery stents), which can reduce the likelihood of both cardiovascular events and deaths.

Finally, the relative risk for oophorectomy is based not on a randomized trial but on the observational, longitudinal NHS study,<sup>2</sup> which may have been subject to selection bias. Were women who went against prevailing wisdom and retained their ovaries at the time of hysterectomy the same ones who had a prevention/wellness view of personal health? Did they follow a regimen of personal fitness and nutrition that reduced their risk of heart disease? In such a scenario, not captured by the statistical controls in the study,<sup>4</sup> the dual facts of ovarian conservation and reduced heart disease are true but unrelated.

**MENZIN:** I agree that the modeling used by Parker and colleagues depends on several reference data sets that have their own potential biases and limitations. For example, the authors recognized that "no published data were found for coronary risk when oophorectomy was performed after menopause," yet their study purportedly demonstrated that the excess mortality associated with oophorectomy between the ages of 50 and 65 years was primarily a result of coronary disease.

The clinical importance of postmenopausal hormone production has not been fully determined. Furthermore, the duration of effective estrogen production in conserved ovaries also can be hard to predict; almost 33% of women experience menopause within 2 years after hysterectomy with ovarian conservation.<sup>10</sup>

The Parker study focuses on mortality; however, the likelihood of medical or surgical intervention for benign or equivocal adnexal pathology also should be considered, along with the potential complexity of such treatments.

## FAST TRACK

**Hysterectomy itself appears to reduce the risk of ovarian cancer by 5% to 15%**

CONTINUED

## ■ Women feel uninformed about their options

**GUZICK:** In my judgment, the fate of the ovaries in a woman undergoing hysterectomy for benign disease should be based on a thorough discussion with the patient that takes into account her individual risk profile and the psychological weight she attaches to the various outcomes. Key factors in the risk profile include age; menopausal status; family history of heart disease and breast and ovarian cancer; and biochemical, genetic, or imaging findings related to cancer, cardiovascular disease, and osteoporosis.

For example, a 45-year-old woman who is lean and normotensive with a favorable lipid profile, and who greatly fears the prospect of ovarian cancer because a friend died of the disease, may choose to have her ovaries removed. Whether this decision is “right” or “wrong” in general is hard to say, but for this patient the decision is acceptable. Her individual risk for cardiovascular disease and osteoporosis can be monitored more carefully and, if necessary, treated effectively early on. She can be given estrogen for vasomotor symptoms.

For postmenopausal women in their early to mid-50s, the situation is murkier, but a blanket recommendation still seems unwarranted. For women in their late 50s and older, although the Parker model shows a “visual” difference between projected survival curves until age 65, it is not clear whether such differences are statistically significant.

**MENZIN:** A critical point was highlighted in a recent description of interviews with women awaiting hysterectomy. Bhavnani and Clarke<sup>11</sup> found that “many women felt inadequately informed about their treatment options and were unaware of important longer-term outcomes of oophorectomy.” Although the work by Parker and colleagues adds another dimension to the counseling of women considering hysterectomy for benign indications, the complexity of that counseling continues to evolve.

Ultimately, the Parker study demonstrates that oophorectomy does not provide a survival benefit over ovarian conservation. This does not mean oophorectomy is always unadvised. Equivalent treatment arms of randomized trials in oncology have demonstrated that quality of life can vary between alternate therapies. Parker and colleagues did not address this critical issue—one I believe to be at the core of every therapeutic decision and informed consent discussion.

In the end, we must individualize the operation to meet the goals and expectations of the patient.

**GUZICK:** I agree. A one-size-fits-all approach to clinical decision-making is rarely appropriate. The study by Parker et al provides a framework for women to determine which size is best for them. ■

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## Oophorectomy does not provide a survival benefit over ovarian conservation