



Editorial

Take 'em or leave 'em: Management of the ovaries in young women with endometrial cancer

The last decade has witnessed a sea change in how gynecologic surgeons approach prophylactic oophorectomy at the time of hysterectomy. Traditional teaching held that the ovaries should be conserved in women <45 years of age and prophylactically removed in postmenopausal women to reduce the risk of ovarian cancer. For premenopausal women in their mid to late 40's, the decision to remove the ovaries was more individualized, but many gynecologists also advocated oophorectomy for women in this age group.

Of late, this traditional approach has been challenged. Data from modeling studies and multiple large, prospective, observational cohorts have suggested that ovarian conservation may be beneficial not only in premenopausal women, but also in postmenopausal women [1–4]. Among women who undergo hysterectomy, ovarian preservation is associated with a reduction in coronary heart disease and all cause mortality [1]. The protective effects of ovarian conservation appear to be greatest in younger women [4]. To date, these data have been derived from studies of women undergoing hysterectomy for benign indications. However, as the incidence of endometrial cancer in younger, premenopausal women is increasing, the question of whether to perform oophorectomy at the time of hysterectomy for young women with uterine cancer is now also being reevaluated.

In this issue of *Gynecologic Oncology*, Lee and colleagues report data for the Korean Gynecologic Oncology Group describing the safety of ovarian conservation in a large cohort of young women with early-stage endometrial cancer. The authors examined 495 premenopausal women with stage I–II, endometrioid endometrial cancer. Within the cohort, 36% of women had ovarian conservation. With a median follow-up of 49 months, the study found no difference in recurrence rates or survival in women treated with or without an oophorectomy. Recurrence rates were 2.3% in those who had ovarian conservation compared to 2.5% in those who underwent oophorectomy, while five-year survival was 94.5% compared to 97.8%, respectively. Importantly, none of the women who had ovarian conservation subsequently developed a primary ovarian malignancy and only one of the recurrences in the ovarian conservation group was in the adnexa [5].

The work by Lee et al. addresses an important clinical dilemma that is occurring with increasing frequency. The study benefits from the inclusion of a relatively large number of women treated at 20 different institutions. Further, the investigators used rigorous methodology to adjust for imbalances in treatment selection to match the women who underwent oophorectomy to those who had ovarian conservation. As the investigators acknowledge however, the decision for ovarian conservation was not randomized and likely still influenced by unmeasured confounding factors. The work provides support for ovarian conservation in young women with endometrial cancer and adds to the growing

body of literature that suggests that ovarian preservation is safe in this population [6–8].

The safety of ovarian conservation in young women with endometrial cancer has been questioned based primarily on two theoretic concerns. First, and perhaps most debated, is the possibility that the ovary harbors occult metastatic disease from endometrial cancer or a synchronous primary tumor of the ovary. Earlier reports of young women with endometrial cancer found ovarian involvement by tumor (metastatic or synchronous primaries) in up to a quarter of women [9]. However, more recent data have suggested that the risk of ovarian involvement is much lower and have used operative findings to stratify risk [6,7]. These studies have noted that the vast majority of women with either synchronous ovarian cancer or metastatic adnexal involvement have either identifiable extrauterine disease at the time of surgery or gross abnormalities of the ovary [6,7]. For women with no clinically apparent extrauterine disease, the risk of ovarian involvement appears to be <1% [6].

The second concern stems from the possibility that continued estrogen production by the ovaries may stimulate residual endometrial tumor cells. This concern is heightened by the fact that young women with endometrial cancer are more likely to have well differentiated tumors which are more likely to express estrogen receptors. Although a potential risk, this fear has largely been assuaged by studies demonstrating the safety of hormone replacement therapy in postmenopausal women with endometrioid endometrial cancer [10].

The prognosis for early stage endometrial cancer, regardless of age, is excellent and most women are likely to be long-term survivors [11]. For women under the age of 60 diagnosed with endometrial cancer, the risk of death from cardiovascular disease is more than six times greater than the risk of death from endometrial cancer [11]. Particularly in young women, in whom endometrial cancer is often associated with obesity and anovulation, the long-term burden of cardiovascular diseases is likely to be substantial and the protective effects of continued endogenous ovarian function potentially beneficial.

From a public health perspective it appears that for many premenopausal women with endometrial cancer, the long-term risks of oophorectomy outweigh the oncologic benefits of the procedure. Based on the available data it seems reasonable to at least consider ovarian preservation for young women with endometrial cancer. The pros and cons of ovarian conservation should be weighed carefully, and consideration should be given to an individual patient's risk of an underlying hereditary cancer syndrome in which case oophorectomy is likely indicated. Women with extrauterine disease or abnormalities of the ovary are at higher risk and should undergo oophorectomy [12]. Although current guidelines recommend oophorectomy for all women with endometrial

cancer, mounting data suggests that it may be time to reevaluate these recommendations and consider more individualized treatment [13].

References

- [1] Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 2009;113:1027–37.
- [2] 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;106:219–26.
- [3] Rivera CM, Grossardt BR, Rhodes DJ, et al. Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause* 2009;16:15–23.
- [4] Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton III LJ. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 2006;7:821–8.
- [5] Lee TS, Lee J-Y, Kim J-W, Oh S, Seong SJ, Lee JM, Kim TJ, Cho CH, Kim S-M, Park C-Y. Outcomes of Ovarian Preservation in a Cohort of Premenopausal Women with Early-stage Endometrial Cancer: a Korean Gynecologic Oncology Group Study. *Gynecol Oncol* 2013;131:289–93.
- [6] Lee TS, Jung JY, Kim JW, et al. Feasibility of ovarian preservation in patients with early stage endometrial carcinoma. *Gynecol Oncol* 2007;104:52–7.
- [7] Pan Z, Wang X, Zhang X, Chen X, Xie X. Retrospective analysis on coexisting ovarian cancer in 976 patients with clinical stage I endometrial carcinoma. *J Obstet Gynaecol Res* 2011;37:352–8.
- [8] Wright JD, Buck AM, Shah M, Burke WM, Schiff PB, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. *J Clin Oncol* 2009;27:1214–9.
- [9] Walsh C, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting ovarian malignancy in young women with endometrial cancer. *Obstet Gynecol* 2005;106:693–9.
- [10] Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2006;24:587–92.
- [11] Ward KK, Shah NR, Saenz CC, McHale MT, Alvarez EA, Plaxe SC. Cardiovascular disease is the leading cause of death among endometrial cancer patients. *Gynecol Oncol* 2012;126:176–9.
- [12] Richter CE, Qian B, Martel M, et al. Ovarian preservation and staging in reproductive-age endometrial cancer patients. *Gynecol Oncol* 2009;114:99–104.
- [13] NCCN. Clinical Practice Guidelines in Oncology: Uterine Neoplasms; 2013 [Version 1.2013].

Jason D. Wright

*Department of Obstetrics and Gynecology,
Columbia University College of Physicians and Surgeons, USA
Herbert Irving Comprehensive Cancer Center,
Columbia University College of Physicians and Surgeons, USA
Division of Gynecologic Oncology, Department of Obstetrics and
Gynecology, Columbia University College of Physicians and Surgeons,
161 Fort Washington Ave, 8th Floor, New York, NY 10032, USA. Tel.: +1
212 305 3410; fax: +1 212 305 3412.
E-mail address: jvw2459@columbia.edu.*

16 July 2013