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Original Article

3 to 5 Years Later: Long-term Effects of Prophylactic Bilateral Salpingectomy on Ovarian Function

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ABSTRACT **Study Objective:** Preliminary data on the effects of prophylactic bilateral salpingectomy (PBS) show that postoperative ovarian function is preserved up to 3 months after surgery. The confirmation of PBS safety on ovarian function even many years after surgery is essential to reassure the medical community that this new strategy, recently proposed for the prevention of ovarian cancer, is at least able to avoid the risk of premature surgical menopause. We investigated whether the addition of PBS during total laparoscopic hysterectomy (TLH) causes long-term effects on ovarian function.

Design: An observational study (Canadian Task Force classification II-3).

Setting: Department of Obstetrics and Gynecology, "Magna Graecia" University, Catanzaro, Italy.

Patients: Seventy-nine patients who underwent TLH plus salpingectomy between September 2010 and September 2012 at our institution have been recalled to be submitted to ovarian reserve evaluation in February 2015. Eight of 79 women refused to participate in this follow-up study.

Interventions: The ovarian age of PBS patients has been determined through OvAge (OvAge sr., Catanzaro, Italy), a statistical model that combines antimüllerian hormone, follicle-stimulating hormone, 3-dimensional antral follicle count, vascular index, flow index, and vascular flow index values. The control group consisted of a large population of 652 healthy women (with intact uterus and adnexa) previously enrolled to build the OvAge model. Comparisons between ovarian ages of PBS patients and the control group have been assessed by analysis of covariance linear statistical modeling.

Measurements and Main Results: The main outcome measurement was the differences in the behavior within OvAge/age relation between PBS and control women. Descriptive statistics of those 71 enrolled PBS patients are the following: age, 49.61 ± 2.15 years; OvAge, 49.22 ± 2.57 years; follicle-stimulating hormone, 43.02 ± 19.92 mU/mL; antimüllerian hormone, 0.12 ± 0.20 ng/mL; 3-dimensional antral follicle count, 1.91 ± 1.28; vascular index, 2.80% ± 5.32%; flow index, 19.37 ± 5.88; and vascular flow index, 0.56 ± 1.12. Analysis of covariance disclosed that PBS and control women do not exhibit different behaviors ($p = .900$) within OvAge/age relation.

Conclusion: According to our model, the addition of PBS to TLH in the late reproductive years does not modify the ovarian age of treated women up to 3 to 5 years after surgery. Journal of Minimally Invasive Gynecology (2017) 24, 145–150 © 2016 AAGL. All rights reserved.

Keywords: Cancer prevention; Long-term follow-up; Ovarian cancer; Ovarian reserve; Prophylactic bilateral salpingectomy; Salpingectomy

Recent literature suggests that many high-grade serous carcinomas develop from the epithelium of the distal fallopian tube and that serous tubal intraepithelial carcinoma represents the putative precursor of these neoplasms [1]. According to the new guidelines of the American Cancer Society and the American College of Obstetricians and Gynecologists [2,3] and considering the new theory on the pathogenesis and origin of these aggressive gynecologic cancers, prophylactic bilateral salpingectomy (PBS) has been suggested as a new preventive strategy for average-risk women not carrying *BRCA* mutations who completed their reproductive desire. The rationale of this approach is that, while eliminating the primary source of cancer, PBS

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in place of standard bilateral salpingo-oophorectomy could also reduce the risk of premature death from cardiovascular disease noted in women subjected to salpingo-oophorectomy before the onset of natural menopause [4].

On the other hand, 2 recent publications about the effect of salpingectomy tubal surgery for hydrosalpinx before in vitro fertilization (IVF) [5,6] recommended laparoscopic salpingectomy or proximal tubal occlusion in cases of surgically irreparable hydrosalpinges to improve IVF pregnancy rates. Although meta-analytic data clearly show that salpingectomy increases the pregnancy rate in women undergoing IVF (relative risk = 2.24; 95% confidence interval [CI], 1.27–3.95) [7], contradictory results are available on the comparison in terms of the ovarian response to hyperstimulation during IVF between patients who did and did not undergo salpingectomy [8].

Preliminary data on the safety of PBS showed that postoperative ovarian function is preserved at least 3 months after surgery [9–11], but to date no evidence of the long-term effects of PBS is available in the literature. The confirmation of PBS safety in ovarian function even many years after surgery is essential for reassuring the medical community that the new proposed preventive strategy is at least able to ward off the risk of premature surgical menopause. Adverse health effects of premature surgical menopause include bone resorption; psychosexual, cognitive, and cardiovascular dysfunction; and increased incidence of fatal and nonfatal heart disease [4].

We previously evaluated the short-term effect of PBS on a population of 79 women subjected to total laparoscopic hysterectomy (TLH) with PBS between 2010 and 2012 [9]. The goal of the current study was to evaluate the ovarian function of these women up to 5 years after the primary surgery to evaluate, for the first time in the literature, the long-term effects of PBS on ovarian function. For this purpose, we used OvAge, a validated generalized linear model that combines a patient's biochemical and 3-dimensional (3D) ultrasonographic values and generates a number that is an estimate of the woman's ovarian age [12].

Materials and Methods

This was an observational study conducted at the Department of Obstetrics and Gynecology, University "Magna Graecia," Catanzaro, Italy, between February and September 2015. The procedures used in the study were in accordance with the guidelines of the Helsinki Declaration. The study protocol was approved by the ethics committee of the Department of Gynecology and Obstetrics, University "Magna Graecia" of Catanzaro.

All patients who underwent TLH with PBS for abnormal uterine bleeding related to benign pathology in our department between September 2010 and September 2012 and provided consent to participate in our retrospective analysis in 2013 [9] were identified and contacted by 2 investigators (M.G.I. and D.L.).

All of these women had undergone TLH and complete bilateral excision of the fallopian tubes. Salpingectomy also had been performed at that time according to the standard technique, thus sparing the mesosalpinx. The tubes had been coagulated and sectioned, beginning from the very distal fimbrial end, carefully preserving the ovarian vascularization, and proceeding toward the uterine cornu.

The following exclusion criteria were used:

1. Patients who experienced acute or chronic pelvic inflammatory disorders; malignant neoplasms; chemotherapy or radiotherapy; autoimmune diseases; or chronic, metabolic, endocrine, and systemic disorders after TLH plus PBS.
2. Patients who had ovarian surgeries after TLH plus PBS.
3. Patients who received estrogen-progestin therapy or metformin in the 2 months before enrollment after TLH plus PBS.

Women with and without menopausal symptoms were analyzed.

The antimüllerian hormone (AMH), follicle-stimulating hormone (FSH), estradiol (E2), 3D antral follicle count (AFC), vascular index (VI), flow index (FI), and vascular flow index (VFI) were measured in all women. In ovulating women, ovarian reserve had been evaluated when early follicular phase was confirmed by the absence at ultrasound of a dominant follicle >10 mm in any of the ovaries in conjunction with the presence of a serum E2 level <60 pg/mL and progesterone <1 ng/mL. Given the poor reliability of the FSH values in the presence of E2 levels >60 pg/mL, data from women with basal E2 levels greater than this cutoff were excluded from analysis, and both patients and women with follicles >10 mm in any of the ovaries or with evidence of corpus luteum were asked to come back 10 to 30 days later according to their previous menstrual histories or the dimension of the preovulatory follicle.

A single experienced investigator (D.L.) performed all of the ultrasound scans using a Voluson-i (GE Healthcare Ultrasound, Zipf, Austria) and a 5- to 9-MHz transvaginal volume transducer, which has 3D ultrasound scanning modes. AFC and VI were measured using a 3D ultrasound data set with a sonography-based automated volume count and virtual organ computer-aided analysis imaging program (SonoAVC, GE Healthcare Ultrasound) as previously described [12].

Intraobserver reliability was expressed as the mean intraclass correlation coefficient (ICC) with a 95% CI. The mean ICCs (95% CI) for the 3D scanning of VI, FI, and VFI were 0.9792 (0.9654–0.9869), 0.8871 (0.7139–0.9719), and 0.9929 (0.9748–0.9967), respectively. The mean ICCs for data acquisition of VI, FI, and VFI were 0.9823 (0.9412–0.9934), 0.9869 (0.9619–0.9934), and 0.9825 (0.9513–0.9977), respectively.