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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.

On the same day of the ultrasonography, blood samples obtained by venipuncture were centrifuged within 30 minutes of collection for 10 minutes at 3500 rpm and 4°C. Aliquots of each serum sample were frozen at −80°C and stored for subsequent assays of AMH, FSH, and E2. To measure serum AMH levels, an AMH-Gen II ELISA assay kit (Beckman Coulter, Brea, CA) was used. The lowest detection limit of AMH is 0.08 ng/mL, and the intra- and interassay coefficients of variation were <3.4% and 4.0%, respectively. An electrochemiluminescence immunoassay method was used to measure the levels of serum FSH and E2 using the COBAS e411 autoanalyzer (Roche Diagnostics, Milano, Italy). The lowest detection limit for FSH was 0.1 IU/L, and the intra- and interassay coefficients of variation were <2.6% and 3.5%, respectively. The lowest detection limit for E2 was 18.4 pmol/L, with intra- and interassay coefficients of variation of 2% and 3%, respectively.

To determine the long-term effect of surgery on each patient's ovarian reserve, we used OvAge, a mathematical formula that takes a patient's biochemical and ultrasonographic values as input and generates an easy-to-interpret number, also called OvAge, which is an estimate of a woman's ovarian age according to the linear relation as follows: OvAge = 48.05 − 3.14*AHM + 0.07*FSH − 0.77*AFC − 0.11*FI + 0.25*VI + 0.1*AMH*AFC + 0.02*FSH*AFC [12]. For obtaining this formula, we previously recruited 652 healthy women, aged 18 to 55 years, with a history of spontaneous conception(s); intact ovaries, fallopian tubes, and uterus; and regular menses with a mean interval of 21 to 35 days to serve as control subjects. Exclusion criteria for the selection of these subjects, enrolled as the training population for the OvAge model, were estrogen or progestin use or breastfeeding in the 2 months before enrollment; pregnancy; history of female infertility; endometriosis; presence of ovarian follicles measuring more than 10 mm according to study entry ultrasonography and other cystic masses of the ovary; history of autoimmune disease; polycystic ovary syndrome [13]; ovarian surgery; gynecologic malignancy; previous radiation or chemotherapy; known chronic, endocrine, systemic, and metabolic disease including diabetes mellitus; hyperandrogenism; hyperprolactinemia and thyroid diseases; hypogonadotropic hypogonadism; and a history of the use of a drug that can cause menstrual irregularity.

In the original OvAge study in women enrolled as healthy fertile controls, the model showed a high level of fit between chronological age and predicted OvAge, meaning that in the absence of risk factors known to be detrimental for ovarian function, chronological age and predicted OvAge are equivalent. Conversely, in patients with known causes of impaired ovarian function, a significant difference between these 2 parameters was shown, indicating that the formula produced was able to recognize pathological deviation from physiologic gonadal activity [12].

For the purpose of the current study, we assumed that if the addition of PBS to TLH did not have any detrimental effect on ovarian function, considering our previous and current exclusion criteria, the predicted OvAge of our 79 patients would be similar to their chronological age. Specifically, if the addition of PBS to TLH does not cause detrimental effects to ovarian function worse than those reported 3 months after surgery [9], differences in behavior within OvAge/age relation between PBS and control women would not be significant.

To summarize data, means and standard deviations or absolute frequencies and proportion were addressed to continuous or count covariates accordingly. To assess differences between OvAge and age within PBS patients versus the healthy control group, analysis of covariance (ANCOVA) linear modeling was used [14]. In all instances, a 0.05 significance level was assumed, and the calculations were performed by R (R Foundation, Vienna, Austria) [15].

Results

From February to September 2015, 79 women were called and asked to participate in this long-term follow-up study. Eight of 79 (10.1%) women refused to participate, leaving 71 patients for the study group. The patients were given the OvAge test, and the results were analyzed. Descriptive statistics of those 71 enrolled women are shown in Table 1.

To confirm the hypothesis that the addition of PBS to TLH did not have any detrimental effects on ovarian function so that the predicted OvAge of our patients would be similar to their chronological age, we proceeded in the following way. We considered the age of a woman to be a continuous response with respect to OvAge and group (i.e., PBS treated or control) covariates. We addressed several statistical models, as explained in Crawley [14]; in particular, we focused on 3 models: an ANCOVA model with interaction between covariates, an ANCOVA model without interaction, and a simpler linear model (i.e., a regression line) over OvAge without group information. Proceeding by a top-down strategy in model selection according to a deviance analysis

Table 1

Descriptive statistics of enrolled women

Parameters	Mean values ± SD
Age at surgery (years)	45.85 ± 2.40
Age at follow-up (years)	49.61 ± 2.15
OvAge at follow-up (years)	49.34 ± 2.12
FSH at follow-up (mU/mL)	43.02 ± 19.92
AMH at follow-up (ng/mL)	0.12 ± 0.20
3D AFC at follow-up (n.)	1.91 ± 1.28
VI at follow-up (%)	2.80 ± 5.32
FI at follow-up (1–100)	19.37 ± 5.88
VFI at follow-up (1–100)	0.56 ± 1.12

3D = 3-dimensional; AMH = antimüllerian hormone; FI = flow index; FSH = follicle-stimulating hormone; SD = standard deviation.

[14], we disclosed that all models are equivalent in a statistical sense. This finding allows us to retain, as a minimal adequate model, the simpler model as shown in Table 2.

The simpler model, the minimally adequate one, exhibits the significant role of the OvAge in estimating women ages and, implicitly, neglects any role of the PBS treatment/control covariate, with a very similar residual standard error (sigma = 4.208 on 729 degrees of freedom) but with an excellent multiple R^2 (0.9885). A deviance analysis confirms the equivalence (p = .986) of 2 models, confirming the hypothesis that the addition of PBS to TLH did not have any detrimental effect on ovarian function (Fig).

Discussion

By means of the OvAge linear model, in the current study we showed that in our population the addition of PBS to TLH in the late reproductive years did not have negative effects on ovarian function, not only a few months after surgery but also 3 to 5 years later. In our patients, ovarian age (or OvAge) was found to be similar to their chronological age because linear models implemented for the statistical analysis showed that there is no difference between treated and untreated groups. Although limited to a well-selected population of women undergoing PBS with TLH in their late reproductive years, this is the first published study reporting information about the long-term effects of salpingectomy performed for cancer prophylaxis.

This finding can be supported by the observation that ovarian blood supply is guaranteed both by infundibulopelvic vessels and by the ovarian branch of the uterine artery, which anastomose with each other at the tubal level [16]. At the time of bilateral salpingectomy, the whole infundibulopelvic blood volume, which was previously distributed between tubes and ovaries, becomes fully available to the ovaries, ensuring adequate gonadal vascularization and maintained ovarian steroid hormone synthesis [16].

In the current study, for the first time in the literature, a long-term evaluation of the effect of salpingectomy on ovarian age has been performed on a cohort of patients who underwent standard TLH with PBS 3 to 5 years earlier. This was possible by using both a new algorithm that combines hormonal and 3D ultrasonographic parameters and a very large population of healthy women as the control group [12]. This sample of 652 healthy fertile women, previously enrolled to generate the OvAge algorithm, is to date the largest data set available for comparing treated and untreated women in terms of ovarian function. It represents the nomogram of reference for the variable "ovarian age," having been built on a population of women deeply screened for all those factors currently known to be able to affect ovarian function. The assumption on which this study is based is that if PBS does not cause significant detrimental effects on hormonal and ultrasonographic ovarian parameters, the ovarian age of the treated patients should not deviate significantly (i.e., as to raise at least 1 OvAge unit/year) from that of women who have never been submitted to this kind of surgery. This assumption was verified by our results; despite a mean 47% decrease in AMH levels from baseline through 3 to 5 years for the 71 PBS women, their OvAge was comparable with that of the control population, meaning that a similar change probably occurs in untreated women in the course of their life.

Fig

Two-dimensional plot for regression analysis. The OvAge control group (gray and white bullets) and the TLH plus PBS treated group (black and dark gray diamonds). In the panel, 3 regression lines have been drawn: a "2-parameter" thin dashed line, with intercept and slope specific for the control group; a "2-parameter" thin continuous line, with intercept and slope specific for the treated group; and, a "1-parameter" solid dashed line, with a common slope (and null intercept) for both groups. All 3 regression lines do not differ in a statistical sense; consequently, the "1-parameter common line" is the minimal adequate model to retain as a valid description of both groups.

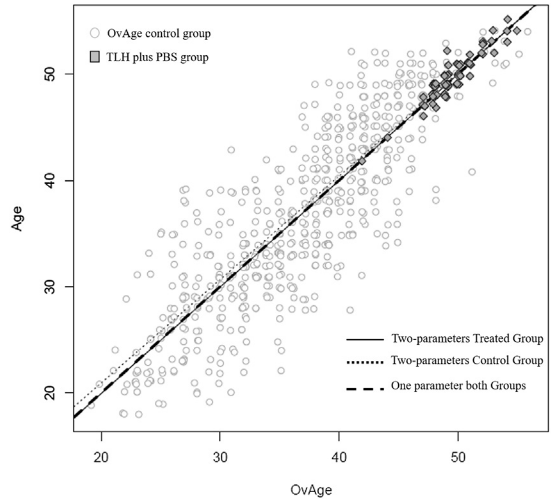

Table 2

Linear models applied

	Estimate	Standard error	p value
Maximal Model			
Intercept	0.1005	0.8474	.906
OvAge	1.0028	0.0225	<.001
Treatment	1.5632	11.2572	.890
OvAge: treatment	0.0286	0.2282	.900
Minimal adequate model			
OvAge	1.0008	0.0040	<.001

Two models are summarized. In model 1, an analysis of covariance with interaction (maximal) model is applied. A simpler model, the minimally adequate one, neglects any role of the treatment/control covariate, with a very similar residual standard error, confirming the hypothesis that the addition of prophylactic bilateral salpingectomy to total laparoscopic hysterectomy had no detrimental effect on ovarian function.

Until now, the effect of PBS on ovarian function was evaluated at only 3 months postoperatively, and the obtained trend was encouraging in all the studies. In 2007, even before the diffusion of the new theory about the tubal origin of most high-grade serous cancers, Sezik et al [17] measured hormonal markers of ovarian function (FSH, LH, and estradiol) to evaluate ovarian reserve of women treated by hysterectomy, and they found no difference among women who underwent salpingectomy versus those who did not. In 2013, we published a retrospective analysis in which the ovarian reserve was not reduced in patients in whom PBS was added to TLH performed for benign uterine pathologies [9]. In our study, ovarian reserve was evaluated by AMH, FSH, AFC, mean ovarian diameters, and peak systolic velocity. In the same year, Findley et al [10], in a pilot randomized controlled trial, used AMH to measure ovarian reserve and concluded that salpingectomy at the time of laparoscopic hysterectomy with ovarian preservation had no short-term deleterious effects on ovarian function.

In 2015, at our institution, women undergoing laparoscopic surgery for uterine myoma or tubal surgical sterilization were randomly subjected to standard salpingectomy or wide mesosalpinx excision [11]. Ovarian function was evaluated by the measurement before and 3 months after surgery of AMH, FSH, 3D indexes, and OvAge for each patient. We found no significant difference between groups, and we speculated that even when the surgical excision includes the removal of the entire mesosalpinx, salpingectomy does not damage the ovarian reserve [11].

Recently, a systematic review and meta-analysis of studies comparing the pregnancy outcomes of patients diagnosed with hydrosalpinx treated with salpingectomy versus those treated with proximal tubal occlusion before IVF showed comparable responses to controlled ovarian hyperstimulation and pregnancy outcomes between the groups [18]. This is an additional demonstration that salpingectomy does not worsen the reproductive prognosis of patients who choose excisional surgery. On the other hand, results on ovarian response to medical induction of superovulation in patients treated by salpingectomy are conflicting [19–21], but authors agree that bilateral salpingectomy has been proven to be a safe procedure at least in terms of surgical outcome and short-term postoperative complications [22]. Moreover, 3 different meta-analyses also reported increased ongoing and clinical pregnancy rates with salpingectomy versus no intervention and no difference in the clinical pregnancy rates between salpingectomy and tubal occlusion [7,23,24].

The strength of the current study is the long-term evaluation, for the first time in the literature, of a well-screened population of women subjected to PBS in the absence of tubal pathologies even in their late reproductive years. All the currently known confounding factors that can interfere with ovarian reserve were listed among the exclusion criteria for both the first [9] and the current study. Reliable and definitive information on the safety of PBS is critically important for the entire medical community, considering that the idea that salpingectomy should be proposed as a preventive strategy for low-risk women who undergo gynecologic surgery is gaining increasing popularity. Moreover, although risk-reducing salpingo-oophorectomy (RRSO) at around age 40 years is currently recommended to women who carry the *BRCA1/2* mutation, an alternative preventive strategy has been put forward for high-risk women—early PBS and delayed oophorectomy (RRO). Although preventive RRSO decreases the ovarian cancer risk by 80% to 96%, based on its short-term and long-term morbidity, which potentially affect quality of life, and on recent insights into the fallopian tube as the possible site of origin of serous ovarian carcinomas, early PBS and delayed RRO could be the best solution.

Recently, a multicenter nonrandomized trial has started enrollment, and participants will choose between standard RRSO at age 35 to 40 years (*BRCA1*) or 40 to 45 years (*BRCA2*) and the alternative strategy of PBS on completion of childbearing and RRO at age 40 to 45 years (*BRCA1*) or 45 to 50 years (*BRCA2*). The aim of the study is to measure menopause-related quality of life but also ovarian/breast cancer incidence, surgery-related morbidity, histopathology, cardiovascular risk factors and diseases, and cost-effectiveness [25].

The increasing interest in PBS as a preventive strategy for both low- and high-risk women and the related crucial importance of long-term follow-up data are confirmed by many Web-based surveys of health professionals' acceptability/attitude toward the new proposal [26–29].

A limitation of our study is the relatively small sample size of women evaluated. However, given the homogeneous distribution of results among this population and considering that this is currently the largest sample of women studied in the literature, the results presented deserve attention. Another limitation of the current study is that the control population is not the same used in the original study [9], that being composed of women treated by standard TLH (with adnexal preservation) between September 2008 and September 2010 matched for uterine weight. Unfortunately, none of these women had undergone an OvAge test at that time, and the gap of average age of at least 2 years makes it impossible to accurately compare that group with the PBS population. Age at menopause of these women will be an interesting outcome for forthcoming analysis, despite the need of consensus for a correct definition for women without a uterus. In this context, further research on the validation of the OvAge model to accurately predict the time to menopause is already in progress.

Another possible limitation of our study is the range of time postoperatively when the subjects were evaluated, which may have created a variable in comparison of the data. However, according to our previous experience [29], when there is evidence of impaired ovarian reserve caused by vascular damage, the modification of biochemical and ultrasonographic parameters is already evident at the 3-month follow-up, and it remains constant at 1 and 2 years. In the same way, reassuring parameters at 3 months do not worsen at the next re-evaluation, allowing us to speculate that the results of the current study are poorly affected by the range of evaluation times.

Furthermore, at surgery and at the time of follow-up, our patients already had evidence of diminished ovarian reserve, given their mean age of 45.97 ± 2.36 and 49.61 ± 2.15 years, respectively. Although it would be better to assess the impact of surgery on younger women in whom ovaries have greater potential for functional loss, unfortunately any assessment of the impact of prophylactic salpingectomy on ovarian reserve is not ethically conducible in patients who have not yet fulfilled their reproductive desire. That is why, to date, in all studies conducted in patients undergoing salpingectomy for cancer prophylaxis, in the absence of tubal pathology and not for reproductive intent, the average age of the population has always been more than 37 years [10,11,17]. Ideally, the same rigorous approach used for women subjected to PBS should be applied on all future studies aimed at evaluating the effect of this kind of surgery in women undergoing IVF to extend the assessable population and to definitively conclude the mid- and long-term safety of laparoscopic salpingectomy.

In conclusion, according to our results, the addition of PBH during TLH in the late reproductive years does not cause ovarian function impairment up to 3 to 5 years after surgery.

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