Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer: A case-control study*

By Cyriel Anthony I. Tingne, MD and Jean Anne B. Toral, MD, MSCE, FPOGS

Department of Obstetrics and Gynecology, Philippine General Hospital, University of the Philippines-Manila

ABSTRACT

Background: Epithelial ovarian carcinoma is the most lethal of the gynecologic malignancies. Recent theories on the etiopathogenesis of epithelial ovarian carcinoma supported the presence of occult, early stage neoplasms in the fimbriated end of the fallopian tube even before development of ovarian carcinoma. This study is interested in correlating opportunistic salpingectomy or tubal ligation as a possible effective prevention strategy in the occurrence of epithelial ovarian carcinoma.

Objective: To determine the association between the occurrence of epithelial ovarian carcinoma and a previous history of tubal ligation and/ or salpingectomy

Methods: This is a case-control study involving chart review of patients who underwent total hysterectomy with bilateral salpingoophorectomy with a histologically verified epithelial ovarian cancer (cases) and patients who underwent same surgical procedure for benign gynecologic conditions specifically myoma uteri and adenomyosis with normal ovaries on final histology report (controls). The association between the occurrence of epithelial ovarian carcinoma and previous tubal ligation and/or salpingectomy was determined using appropriate statistical methods.

Results: A total of 558 patients were included in this review. They were divided into 158 post-surgical patients with histologically verified epithelial ovarian cancer (cases) and 400 post-surgical patients for benign gynecologic conditions with normal ovaries on final histology report (controls). Adjusted for age, parity and obesity the odds of developing epithelial ovarian carcinoma in subjects without previous tubal ligation and/or salpingectomy is 29%.

Conclusion: The result of the study showed that tubal ligation and/or salpingectomy reduces the risk of developing epithelial ovarian carcinoma hence for patients at average risk of ovarian cancer, risk-reducing salpingectomy should be discussed and at the time of abdominal or pelvic surgery. It must also be included in the counseling of women planning a hysterectomy for benign indications to conserve ovarian function and prevent ovarian epithelial carcinoma.

Keywords: epithelial ovarian carcinoma, tubal ligation, prevention

INTRODUCTION

Epithelial ovarian carcinoma is the most lethal of the gynecologic malignancies. The American Cancer Society estimates that 21,980 women will be diagnosed with ovarian cancer in the United States, and 14,270 will die of the disease in 2015.[1] At present, there has been no effective screening test, and treatment of advanced stage ovarian carcinoma has yielded marginal survival rates. Therefore, the development of prevention strategies may prove to be the only modality that will give favorable impact on this dreadful disease.

Recent theories on the etiopathogenesis of epithelial ovarian carcinoma supported by molecular, morphological and immunohistochemical studies categorizes epithelial ovarian carcinoma into Type I and Type II based on a dualistic model of carcinogenesis. Type I ovarian malignancies progress in a step-wise fashion beginning as a low grade lesion and later on developing into a malignancy. They are usually indolent, genetically stable and harbors specific mutation including KRAS, BRAF, ERBB2, CTNNB1, PTEN, PIK3CA, ARID1A, and PPP2R1A. Type I tumors comprise low-grade serous, low-grade endometrioid, clear cell and mucinous carcinomas, and Brenner tumors. Type II ovarian malignancies on the other hand is characterized to have high genetic instability, aggressive, present in an advanced stage and have a high frequency of TP53 mutations. Type II tumors comprise high-grade serous, high-grade endometrioid, malignant mixed mesodermal tumors (carcinosarcomas), and undifferentiated carcinomas. In women with BRCA1 and BRCA2 mutations, for which adnexal surgery was done, histopathologic results

*2nd Place, 2017 Philippine Obstetrical and Gynecological Society (POGS) Research Paper Contest, April 6, 2017, Citystate Asturias Hotel, Puerto Princesa City, Palawan

showed the presence of occult, early stage neoplasms in the fimbriated end of the fallopian tube even before development of ovarian carcinoma. These so called serous tubal intraepithelial carcinomas (STIC) are early tubal lesions mostly found in the fimbriated end of the fallopian tube specifically in the secretory type cells. Shedding of this precursor lesions on the ovarian surface therefore suggest the pathogenesis of ovarian carcinoma. Serous tubal intraepithelial carcinoma (STIC) lesions in the fallopian tubes have not only been found in women with known BRCA mutations but they also in 50% to 60% of sporadic serous ovarian cancers. Furthermore, these serous tubal intraepithelial carcinomas are known to harbor the same TP53 mutations found in concomitant ovarian carcinomas implicating a clonal relationship.[2]

In light with the current findings on the origin of ovarian carcinoma, opportunistic salpingectomy or tubal ligation may therefore be an effective prevention strategy. Several studies have shown that tubal ligation and salpingectomy reduces the risk of developing epithelial ovarian carcinoma. In a study by Madsen et al in 2015, a nationwide registry-based case control study which involved 13,241 Danish women diagnosed with epithelial ovarian cancer and 3,605 women with borderline ovarian tumor from 1982-2011, results have shown that tubal ligation reduced overall epithelial ovarian cancer risk (odds ratios 0.87; 95% confidence interval 0.78-0.98) with significant variation according to histology with the strongest risk reduction associated with endometrioid cancer (odds ratios 0.66; 95% confidence interval 0.47-0.93).[3] In a population-based cohort study by Falconer et al in 2015, which involved 251,465 Swedish women with previous surgery for benign gynecologic condition comparing it to the 5,449,199 unexposed women from 1973 to 2009, results showed that there was a statistically significant lower risk for ovarian cancer among women with previous salpingectomy (HR=0.65, 95% CI=0.52) when compared to the unexposed population. In the same study, bilateral salpingectomy was associated with a 50% decrease in risk of ovarian cancer compared with the unilateral procedure (HR= 0.35, 95% CI= 0.17 to 0.73).[4] Two meta-analysis have also shown that tubal ligation reduces the risk of epithelial ovarian carcinoma. In 2012, a meta-analysis done by Rice et al. on 30 studies on tubal ligation and 24 studies on hysterectomy from 1969 to 2011 was done. The analysis found out that tubal ligation decrease the risk of ovarian carcinoma with a relative risk of 0.70 (95% CI: 0.64, 0.75). In secondary analysis of the study, the association between tubal ligation and ovarian cancer risk was stronger for endometrioid tumors (RR= 0.45, 95% CI: 0.33, 0.61) compared to serous tumors. This study also concluded that observational epidemiologic evidence supports that tubal ligation and hysterectomy are associated with a decrease in the risk of ovarian cancer by approximately 26-30%.[5] In a 2011 meta-analysis, Cibula et al concluded that previous tubal ligation in women at average risk for ovarian cancer was associated with a 34% overall risk reduction; however, no significant risk reduction was found for women with mucinous or borderline tumors who had undergone previous tubal ligation.[6]

OBJECTIVES

The purpose of this study is to determine the association between the occurrence of epithelial ovarian carcinoma and a previous history of tubal ligation and/ or salpingectomy

SPECIFIC OBJECTIVES:

1. To determine the sociodemographic profile of both cases and controls.
2. To determine the odds ratio in developing epithelial ovarian carcinoma with history of tubal ligation and/ or salpingectomy.
3. To analyze the association of previous history of tubal ligation and/ or salpingectomy in the occurrence of epithelial ovarian carcinoma.
4. To determine which histologic subtype of epithelial ovarian cancer is associated with highest risk reduction rate for patients with a history of tubal ligation and salpingectomy.
5. To determine the interval time and age of patient from bilateral tubal ligation or salpingectomy to diagnosis of ovarian cancer.

METHODS

This is a case-control study conducted from September to October 2016. The study involved chart review of patients who underwent total hysterectomy with bilateral salpingoophorectomy with a histologically verified epithelial ovarian cancer (cases) and patients who underwent same surgical procedure for benign gynecologic conditions specifically myoma uteri and adenomyosis with normal ovaries on final histology report (controls).

Medical records of the eligible cases and controls from January 2012 to December 2015 were retrieved and reviewed. The principal investigator retrieved patient information and data checklist documenting demographics (age, height and weight), risk factors (gravidity, parity, obesity, pelvic endometriosis, and polycystic ovarian syndrome) and history of tubal ligation and salpingectomy and the year and age of the patient when it was performed. A master list was utilized as a guide during data collection with the subjects included in the study being assigned to their corresponding study

number. The indication and complete surgical procedure were also documented. The complete histologic diagnosis was obtained including the specific histologic subtype of epithelial ovarian cancer. The association between the occurrence of epithelial ovarian carcinoma and a previous tubal ligation and/ or salpingectomy was determined using appropriate statistical methods.

STATISTICAL ANALYSIS

After the data has been extracted by the investigator from the patient charts, all the information were manually entered into an electronic spreadsheet file and subsequent data processing and analysis was carried out using the software Stata 13.0.

Descriptive statistics such as mean and standard deviation for continuous variables such as age, BMI, gravidity and parity; or frequency and percentage were used for the categorical data variables such as disease status, presence of PCOS, and obesity to provide an overview of the study population. A Chi-square test of association or independent t-test, whichever is applicable, was done to determine if there is a significant difference in the baseline clinico-demographic variables between the study groups. Proportion per categories of the qualitative variable such as presence of PCOS, obesity, etc. was also described. Point and interval estimates of the proportion for those who underwent tubal ligation or salpingectomy were also determined. In order to determine procedure-specific proportions, those participants who previously had the procedures were further divided among those who underwent tubal ligation and salpingectomy.

The exposure odds was computed to determine the association of the performance of said procedures among cases and controls; and subsequently determine the odds ratio for the exposure and outcome of interest. Logistic regression was done mainly with the adjustment for probable confounders to be conducted using select clinical variables based on literature through the backward elimination process. An arbitrary cut-off change in p-value of less than 0.25 was used to screen for probable confounders, and significant confounders were identified based on the change in estimation criterion where in the cut-off value is 10%. If the change in estimate is greater than 10%, it will be included in the final model, otherwise it will be removed.

The level of significance for all sets of analysis was set at $p<0.05$ using two-tailed comparisons. Significance levels were adjusted for multiple comparisons performed, if applicable.

RESULTS

Data collection of this study identified a total of 158 eligible cases with epithelial ovarian cancer and 400 eligible controls. Table 1 shows the characteristics of both cases and controls. For both cases and controls majority of women at the time of diagnosis of the disease were ages 41 to 50 years old, 58 (36.71%) and 286 (71.5%) respectively. Socio demographic profile also shows that majority of both cases and controls are women who have had two or more pregnancies. At the same time, it can be noted that there were more nulliparous women among the cases than otherwise. Among controls, 63 out of 400 (67.02%) were identified to have pelvic endometriosis while 58 out of 400 (57.79%) have history of polycystic ovarian syndrome and most surgeries were done for myoma uteri, 347 (98.58%). Among cases, the epithelial subtype most commonly identified was serous carcinoma, 51 (32.28%) followed by mucinous type, 43 (27.22%), endometrioid, 40 (25.32%) and clear cell, 24 (15.19%). Of the eligible cases, 16 out of 158 (10.13%) with history of tubal ligation while 41 out of 400 (10.25%) controls with prior tubal ligation. Table 2 shows the association of tubal of ligation and subtype of epithelial ovarian carcinoma and the time and age since the procedure was done, it can be seen that for patients with mucinous, serous, endometrioid and clear cell epithelial ovarian carcinoma, 10 out of the 43, 4 out of the 51, 1 out of 40 and 1 out of 24 had a history of tubal ligation respectively. The table also shows that most tubal ligation was performed when the patient's age was less than 35 and that the time elapsed since tubal ligation until the development of the disease was 10 to 19 years. Table 3 shows the regression analysis of epithelial ovarian carcinoma and history of tubal ligation and salpingectomy, adjusted for age, parity and obesity it is shown that the odds of developing epithelial ovarian carcinoma increases by 29% in the absence of previous tubal ligation and/or salpingectomy.

DISCUSSION

Epithelial ovarian carcinoma is the most lethal of the gynecologic malignancies.[7] Despite holistic scientific innovations in surgical technique and chemotherapy, including targeted therapy and antiangiogenic agents, the overall survival rate has not improved over recent decades.

To reduce the impact of ovarian cancer on women's health, there is a need to detect it in an early stage and also prevent it from occurring. Options to detect it early include periodic clinical examination, transvaginal sonography and estimation of serum CA-125 level, but these have not been found to be uniformly effective.[7] Ovarian cancer has been called a 'silent abdominal tumor' because symptoms such as abdominal distension, nausea and early satiety due to the presence of ascites, and peritoneal/omental metastases occur late in the course of the disease.

Table 1. Characteristics of both cases and controls

Characteristics	Cases (n=158)	Controls (n=400)	p-value
Age in years			
21 to 30	6 (3.80%)	2 (0.50%)	
31 to 40	22 (13.92%)	12 (3%)	
41 to 50	58 (36.71%)	286 (71.50%)	0.00**
51 to 60	55 (34.81%)	94 (23.50%)	
61 to 70	14 (8.86%)	6 (1.50%)	
71 to 80	3 (1.90%)	-	
Parity			
None	42 (26.58%)	76 (19.10%)	
Uniparous	18 (11.39%)	48 (12.06%)	0.05*
Two and above	98 (62.03%)	274 (68.84%)	
Obese	27 (17.09%)	139 (34.75%)	0.00**
Tubal Ligation	16 (10.13%)	41 (10.25%)	0.97
Endometriosis	-	63 (67.02%)	
Polycystic ovarian syndrome	-	58 (59.79%)	
Myoma uteri	-	347 (98.58%)	
Adenomyosis	-	115 (78.23%)	
Histologic Subtype			
Clear cell	24 (15.19%)	-	
Endometrioid	40 (25.32%)	-	
Mucinous	43 (27.22%)	-	
Serous	51 (32.28%)	-	

Table 2. The association between tubal ligation and the risk of epithelial ovarian cancer and histologic subtype by the time since tubal ligation and age at tubal ligation

Characteristics	Endometrioid	Endometrioid	Mucinous	Serous	p-value
No tubal ligation	23 (95.83%)	39 (97.50%)	33 (76.74%)	47 (92.16%)	0.01*
Age during procedure					
<35	1 (100%)	1 (100%)	7 (70%)	4 (100%)	0.68
≥35	-	-	3 (30%)	-	
Time since tubal ligation					
1 to 9	-	-	-	-	
10 to 19	-	-	8 (80%)	1 (25%)	0.09
20 and above	1 (100%)	1 (100%)	2 (20%)	3 (75%)	

Table 3. Regression analysis of epithelial ovarian cancer and history of tubal ligation or salpingectomy

Characteristics	Unadjusted Odds		Adjusted Odds	
	OR (95% CI)	p-value	OR (95% CI)	p-value
No history of the procedure	1 (0.19 to 6.94)	0.99	1.29 (0.25 to 6.78)	0.76
Age in years	1.03 (0.95 to 1.11)	0.48	1.03 (0.95 to 1.12)	0.44
Obesity	2.11 (0.14 to 30.89)	0.46	2.32 (0.27 to 19.79)	0.44
Parity				
None	1.00		1.00	
Uniparous	0.75 (0.12 to 4.66)	0.76	0.64 (0.10 to 4.15)	0.64
Two and above	0.88 (0.22 to 3.54)	0.85	0.75 (0.17 to 3.26)	0.69

Recent data suggest that some ovarian cancers are actually initiated in the fallopian tubes, thus removal of the fallopian tubes or cutting a segment of it (bilateral salpingectomy and tubal ligation) may be a risk-reducing strategy in both high-risk and average-risk women. Pre-invasive lesions in the distal fallopian tubes [serous tubal intraepithelial neoplasia (STIN)] have been identified in 1 to 6% of high-risk women undergoing risk reducing BSO[8]. Serous tubal intraepithelial carcinoma (STIC), and invasive serous carcinomas are also identified in the distal fimbrial end of the fallopian tubes in women with non-familial or sporadic 'ovarian' cancer. These lesions originating in the tubal fimbria may spread to the peritoneum and result in apparent primary peritoneal carcinoma without an ovarian lesion. Thus, serous ovarian, fallopian tubal and peritoneal carcinomas are regarded as a single entity and designated as 'pelvic serous carcinoma'. Based upon these findings, it is proposed that tubal neoplasia is the primary lesion in high-grade serous pelvic carcinomas and that these lesions subsequently spread to the ovary and peritoneum. Results of this study showed that the odds of developing epithelial ovarian carcinoma increases by 29% in subjects without previous tubal ligation and/or salpingectomy. This extrapolation is consistent with several published literatures as cited in this paper on the role of tubal ligation and salpingectomy in reducing the risk of developing epithelial ovarian carcinoma. Although this study is limited because of its small sample size and retrospective method, a larger sample size and prospective data collection of at least 10 years may be employed in future studies to determine long term impact of risk-reducing salpingectomy as a current primary prevention strategy for women against ovarian cancer.

CONCLUSION

The result of this paper showed that tubal ligation and/or salpingectomy reduces the risk of developing epithelial ovarian carcinoma hence for patients at average risk of ovarian cancer, risk-reducing salpingectomy/tubal ligation should be discussed and at the time of abdominal or pelvic surgery. It must also be included in the counseling of women planning a hysterectomy for benign indications to conserve ovarian function and prevent ovarian epithelial carcinoma. Additional studies preferably prospective follow up and a larger sample size must be employed in the future to find out the role of risk-reducing salpingectomy as a current primary prevention strategy for women against ovarian cancer. ■

REFERENCES

1. Walker JL, Powell CB, Chen LM, Carter J, Bae Jump VL, Parker LP, Borowsky ME, Gibb RK. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. *Cancer.* 2015. July 1; 121(13):2108-20.

2. Kurman RJ, Shih IM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer – shifting the paradigm. *Human Pathology*. 2011. Jul 31; 42(7):918-31.

3. Madsen C, Baandrup L, Dehlendorff C, Kjær SK. Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: a nationwide case – control study. *Acta Obstetricia et Gynecologica Scandinavica*. 2015. Jan 1; 94(1):86-94.

4. Falconer H, Yin L, Grönberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. *Journal of the National Cancer Institute*. 2015. Feb 1; 107(2):dju410.

5. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: a meta-analysis. *Journal of Ovarian Research*. 2012. May 15; 5(1):1.

6. Cibula D, Widschwendter M, Májek O, Dusek L. Tubal ligation and the risk of ovarian cancer: review and meta-analysis. *Human Reproduction Update*. 2011. Jan 1; 17(1):55-67.

7. Woodward ER, Sleightholme HV, Considine AM, Williamson S, McHugo JM, Cruger DG. Annual surveillance by CA125 and transvaginal ultrasound for ovarian cancer in both high-risk and population risk women is ineffective. BJOG: *An International Journal of Obstetrics & Gynaecology*. 2007. Dec 1; 114(12):1500-9.

8. Bagga R. Remove the Fallopian Tubes and save the Ovaries: The Emergence of Opportunistic Salpingectomy to reduce Ovarian Cancer Risk.