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Research Article

Effect of Prior Tubal Ligation on Peritoneal Cytology and Survival in Endometrial Cancer Patients

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Abstract

Background: Endometrial carcinoma is the most gynecologic cancer and its disseminations are via lymphatic, vascular and exfoliation. A diffusion exfoliating pathway to the peritoneal cavity is provided through the fallopian tubes. Bilateral tubal ligation is one of the most common ways of birth control, and only three studies have demonstrated the correlation between tubal ligation and endometrial carcinoma and eventually this association is still not definitely clear. Therefore, we have studied the influence of prior tubal ligation in positive rate of peritoneal cytology and other prognostic factors.

Materials and Methods: This retrospective cohort study was conducted on 174 endometrial cancer patients in 2017 at Emam Hospital of Tehran, Iran. Patients were divided into two groups based on whether they had previously had the surgery of tubal ligation or not. All calculated P values were 2-sided, and $P < 0.05$ was considered statistically significant.

Result: Of the 174 patients, 173 completed follow up, with 28% undergoing prior tubal ligation (TL) and 71% not.

There was no difference in the grade of cancer cells in the two groups. In the TL group, the rate of recurrence was 14.9% and in the other group was 19.8%, although this difference was not significant. Rate of distant metastasis was 6.4% in TL group and 10% in another group. In TL group, mortality rate was 12.5% and in another group was 15.2%. Those differences were not significant either. **Conclusion:** This study shows that endometrial cancer patients with prior tubal ligation had lower rate of deep myometrium invasion, lymph vascular space invasion and positive peritoneal cytology. The TL group was more likely to be in the early stages, maybe due to the factors mentioned above. Accordingly, prior TL can be introduced as a preventive factor for advanced endometrial cancer, but more studies are needed.

Keywords: Tubal ligation, Recurrence, Endometrial carcinoma

Introduction

Endometrial cancer is the most common malignancy and is often discovered in the early stages. But the prognosis of recurrence and intra-peritoneal dissemination is poor [1]. The variables that affect extra uterine spreading of tumor, have roles in the survival rate [2]. In a study, based on multivariate analysis, it was shown that positive peritoneal cytology (PPC) is a prognostic factor for distant metastases [3]. While in other studies it was demonstrated that PPC alone does not have any effect on prognosis. Thus, in 2009 The International Federation of Gynecology and Obstetrics (*FIGO*), removed PPC from surgical staging of endometrial cancer although it stressed that peritoneal cytology should be documented in all patients [4].

After the removal of peritoneal cytology from staging, other studies were designed and they showed that PPC is an independent factor for prognosis of endometrial cancer in early stages [5-8]. The fallopian tube ligation at the beginning of the laparoscopic surgery in endometrial cancer is performed in order to prevent malignant cells from spreading into the intra-peritoneal cavity, during manipulation [9]. The mechanism of cell dissemination via the fallopian tubes is not yet well known. In the large volume study with 4489 subjects, prior TL was inversely related to incidence of advanced stages and rate of PPC. The mortality rate was less than the other group which does not have the history of TL. Statistical analysis demonstrated that the effect of TL on mortality was because of its influence on the stages. In this regard, different types of TL

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were not compared [10]. In another study, the findings show that prior TL might influence metastatic spread of non-endometrioid endometrial cancer due to prevent the dissemination of malignant cells into intra peritoneal cavity.

So, by looking at these results we find that the association between bilateral tubal ligation and endometrial cancer patients outcome is not yet known clearly and definitely. Endometrial cancer is the most common gynecologic cancer and bilateral tubal ligation is also one of the most popular contraception methods which has been used worldwide in recent years. Therefore, we have studied on the correlation between endometrial cancer and prior tubal ligation which have been reported in only three previous English studies. Additionally, in this study, we decided to check the effect of TL on the rate of PPC and other risk factors such as lymph vascular space invasion (LVSI) and deep myometrium invasion in endometrial cancer which is based on our knowledge, so far, no studies have been done about it.

Material and Method

This retrospective cohort study was conducted on 174 endometrial cancer patients who were referred to Gynecology Oncology Ward of Imam Khomeini Hospital of Tehran University of Medical Sciences, Tehran, Iran, from 2009 to 2012 and a five-year period was considered for follow up. This was as a pilot study only in our center and, the sample size of the study was low. This study was done in 2017 at Emam KHomeini Hospital of Tehran, Iran. Authorization to conduct this study at the University Research Committee was registered. At Imam Khomeini Hospital as a routine, at the onset of admission, patients fill the consent form in which the patient allowed us to use her file for future research. In this study patients name were not mentioned at any stages of the work and obviously there was no intervention because, our study was a retrospective cohort. However, for this research, it was authorized by the Ethics Committee of the University and the code number is IR.TUMS.IKHC.REC.1396.2474.

Our inclusion criteria were the patients with endometrial carcinoma whose cancer was detected by endometrial sampling or fractional curettage who were treated with Hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing and lymph node sampling if, the cancer was in the early stages and cytoreductive surgery in advanced stages. Our exclusion criteria included the following: The patients, who received neo-adjuvant chemotherapy before surgery, neo-adjuvant pelvic irradiation before surgery, patient in FIGO stage four at initial diagnosis (distant metastasis) and, incomplete files. The stages of disease based on *FIGO Staging for endometrial cancer 2009*, histo pathological nuclear grading, and result of peritoneal cytology were recorded in the files, were extracted and then entered the software $SPSS_{v22}$ (IBM SPSS, Armonk, NY, USA), and patients were divided into two groups based on whether they had previously had the surgery of tubal ligation or not. Our variants included the following: recurrence rate, distant metastases rate, mortality rate, and rate of LVSI, stage of cancer, PPC, grade, and deep myometrium invasion in two groups. The descriptive statistics were conducted as absolute and relative frequency based on the purpose of the analysis; the mean and standard deviation for quantities variables were considered. Distributions of LVSI, stages of the cancer, PPC, deep myometrium invasion and grade of the cancer cells were compared between two groups. The data are collected by a researcher in a predefined questionnaire, then, based on the goals (recurrence and metastasis rates) the analysis was carried out. Descriptive statistics including absolute and relative abundance were used for qualitative variables and, the mean and standard deviation were used for quantitative variables. For the purpose of comparing the outcome of recurrence and metastasis between the two groups,$\chi 2$ test was used. All calculated P values were 2-sided, and $P < 0.05$ was considered statistically significant. Our sample size formula with confidence interval 95% and the power of 80% was calculated to be at least 72 patients as the minimum sample size in each group. We used Mingxia's study to determine the sample size.

Result

Of the 174 patients, 173 completed follow up. 49 patients (28%) had a history of prior TL and 125 patients (71%) did not have. In general, the number of patients in stage 1, 2, 3 and 4 were 118, 16, 26 and 14, respectively. Recurrence rates after 5-year-follow up were reported 18.5% and 85%of all the patients were alive. The rate of LVSI was 35% and deep myometrium invasion was seen in 71 cases (40.8%). PPC was obtained in 26 cases (15%) then the patients were divided into two groups as they had previously undergone TL. There was no significant difference between the two groups in frequency of pathologic grading (Table 1). Recurrence rate in TL group and another one were reported 14.9% and 19.8%, respectively. But it was not significant (P=0/459). Rate of distant metastasis was 6.4% in TL group and 10% in another group. In the TL group, mortality rate was 12.5% and in the other group was 15.2%. The differences were not significant either (P=0/462, P=0.651 respectively). In TL group LVSI rate was 25% and in another group was 39.8%, P=0.069 (Table 2). Deep myometrium invasion was detected in 32.6% of cases in TL group and in 45.2% of the group without history of TL (P=0.09) (Table 3). There is a significant difference of PPC rate between two groups, 2%, 20% and, P=0.03 (Table 4). Finally, for the abundance of disease stages, the group on which

Grade Scoring	TL*(yes)	TL*(no)	P value
Grade 1	19 (38%)	44 (35.5%)	0.571
Grade2	10 (20.4%)	35 (28.2)	
Grade 3	20 (40.8%)	45 (36.3%)	

*tubal ligation

Table 1: The relationship between TL and grade of endometrial cancer as shoeing in the table, there is not a significant correlation between two groups in grading of endometrial cancer.

LVSI*	TL**(yes)	TL**(no)	P value
Yes	12 (25%)	49 (39.8%)	0.069
No	36 (75%)	74 (60.2%)	

*Lymph vascular space invasion, **tubal ligation

Table 2: The relationship between TL and lymph vascular space invasion (LVSI). Although the rate of LVSI is lower in TL group than other one, but it is not significant.

Myometrium invasion	TL*(yes)	TL*(no)	P value
<50%	31 (67.4%)	68 (54.8%)	0.096
>50%	15 (32.6%)	56 (45.2%)	

*tubal ligation

Table 3: The association between TL and deep myometrium invasion (invasion>50%) although the rate of deep myometrium invasion is lower in TL group than other one, but it is not significant.

PPC*	TL**(yes)	TL**(no)	P value
yes	1 (2%)	25 (20%)	0.03
no	48 (98%)	100 (80%)	

* Positive peritoneal cytology, **tubal ligation

Table 4: The association between TL and positive peritoneal cytology, this table shows that in TL group, the rate of intra-abdominal spreading of cancer cell or PPC is lower compared to another group, and this correlation was statistically significant.

stage	TL*(yes)	TL*(no)	P value
1	39 (88.6%)	79 (67.5%)	0.02
2	0 (0%)	12 (10.3%)	
3A	1 (2.3%)	4 (3.4%)	
3B	3 (6.8%)	3 (2.6%)	
3C	1 (2.3%)	10 (8.5%)	
4	0 (0%)	9 (7.7%)	

TL*: tubal ligation

Table 5: The association between TL and frequencies of disease stages. Finally, for the abundance disease stages, that group who were performed prior TL, incidence of stage 1 of cancer was the most (88.6% vs 67.5%, P=0.02)

prior TL was performed, had more incidence of stage 1 with the result of 39%, P=0.02 (Table 5).

Discussion

Endometrial cancer is the most common gynecologic cancer in the world. There are numerous factors affecting the recurrence rate and survival of the cancer such as grading and FIGO staging of the tumor, LVSI, deep myometrium invasion and, PPC. Advanced stages, (three and four) are associated with higher rate of recurrence and lower survival. Patients with grade 3 are also at higher risk. Invasion of tumoral cells into the microscopic lymphatic vessels is related to poor prognosis. Patients, in whom the tumoral location is limited to superficial layer of the underlying myometrium, have a better survival than others. Eventually, positive peritoneal cytology at initial diagnosis is another risk factor of survival although the recent factor is controversial [11-13]. Bilateral tubal ligation is one of the most common Contraception methods used universally. One of the ways of spreading cancer cells is exfoliation via fallopian tubes. So, the aim of our study was to investigate the effect of prior TL on the prognostic factors of endometrial cancer.

The study on 4489 patients with endometrial cancer demonstrated that prior TL is associated with advanced stages and intra-peritoneal spread of cancer, inversely; and due to the stage of the disease, it decreases mortality [10]. In the present study, prior TL was associated with early stage of endometrial cancer and lower rate of PPC or on the other hand, lower rate of intraperitoneal spreading. PPC rate in TL group and the other one were reported to be 2% and 20% respectively, (P=0.03). For the abundance of disease stages, the group on which prior TL was performed, incidence of stage 1 of cancer was the most: 39%, (P=0.02). Our result was the same as the recent study.

In another study patients with history of prior bilateral TL, were diagnosed at lower tumor stages and mortality was reduced [14].

In another study with 562 cases, TL was related to the lower rate of PPC, and lower recurrence rate of endometrial cancer in non endometrioid subtypes [15]. In our study, TL was also significantly associated to lower rate of PPC. In terms of relapse rate, we found that TL group had lower recurrence than the other group, recurrence rate in TL group and another one were reported 14.9% and 19.8% respectively. But it was not significant (P=0/459). Rate of distant metastasis was 6.4% in TL group and 10% in the other group. In TL group, mortality rate was 12.5% and in the other group was 15.2%. The differences were not significant, either. (P=0/462, P=0.651 respectively.) Substantially, we also discovered lower rate of recurrence, distant metastasis and mortality in TL group even though these were not statistically significant they can be important clinically.

In the large recent study on 93,676 women from 40 clinical centers, the relationship between bilateral tubal ligation and risk of endometrial cancer was discussed. They finally reported that there is no relationship between TL and individual baseline risk of endometrial cancer. This study was the largest patient cohort in this field but did not mention the role of TL on the recurrence rate and other risk factors in endometrial cancer [16].

In this research, for the first time we studied the effect of prior TL on deep myometrium invasion, LVSI and PPC as the prognostic factors of endometrial cancer. Our data showed that prior tubal ligation is associated with lower LVSI rate, deep myometrium invasion rate and PPC rate. In spite of the fact, there were not statistically significant associations in the first two factors, PPC was significant, these data can be clinically interesting and important. We found that TL group was more likely to be in the early stages of the disease.

The rate of relapse and mortality, however, was lower but not significant, and its insignificance, was perhaps due to the small number of patients who were studied. But rate of recurrence, distant metastasis and finally the mortality rate are, substantially, three important parts of each cancer outcome and can be important clinically.

As shown in recent studies, lumen of the fallopian tubes is a path of exfoliation of malignant cells into the peritoneal cavity [17,18]. When this lumen is ligated, this path abrupt, and because of this, the rate of PPC is reduced by TL, which is also confirmed in this study. When TL is done, blood and lymphatic vessels are also interrupted, whether the closure of these vessels causes changes in the entire microscopic vessels of the uterus, is still unclear, but such a change might occur after TL in the uterine tissue. In the TL group the grade of malignant cells is not different from the other group, but we see that it is effective on the lower spread of malignant cell via myometrial and lymphatic vessels. In other words, TL reduces LVSI and deep myometrial invasion in addition to preventing the exfoliation. Perhaps the reason of the fact which was reported that the more prevalence of early stage diagnosis in TL patients, would be the lower invasion to myometrium and LVSI. We concluded that prior TL could have a positive prognostic effect by reducing in PPC, LVSI and deep myometrium invasion rate. Our study limitation was that two histopathologic subgroups, endometrioid and non-endometrioid were not compared against. These two subgroups are very different and the results may not be the same. Another limitation of our study referred to the entity of a retrospective cohort study such as probable biases, like any other cohort studies.

Conclusion

Further studies are needed to validate our hypothesis.

Comparison of the hysteroscopic method of tubal ligation in which the tubes and vessels are not interrupted and only the lumen is closed, with the conventional method of tubal ligation can be promising.

Our recommendation is that further studies should be done to evaluate the protective effect of TL in endometrial carcinoma.

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Conflict of Interest

All authors have not any conflict of interest to declare.

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