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Full Length Research Paper

Effect of opportunistic salpingectomy on ovarian reserve in patients undergoing hysterectomy for benign indications

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Epithelial ovarian cancer is the gynecologic cancer with the highest mortality in the western world. Distal part of tuba uterine is accused of being the origin of this cancer type. Thus, prophylactic salpingectomy has been suggested by several societies however this procedure can also cause early ovarian ageing. We aimed to elucidate the effect of salpingectomy additional to hysterectomy on ovarian reserve appraising ultrasonographic scanning and AMH. Prospective, randomized analytical study is achieved comparing patients who have underwent solely hysterectomy (N:29) and underwent hysterectomy and prophylactic salpingectomy (N:34). Comparison of AMH values between groups did not differ statistically significant whereas pre-operative and post-operative values of AMH were significantly decreased in both groups. Comparison of ovarian volume and AFC did not differ statistically significant. Ovarian blood flow doppler ultrasonography parameters were (PSV, PI) generally (10/12 parameters) did not differ significantly between groups. Prophylactic salpingectomy during hysterectomy did not cause additional ovarian reserve impairment without any operative and post-operative complications. Patients scheduled hysterectomy for benign reasons, could be informed about retained fallopian tubes and the benefit and harm of prophylactic salpingectomy precisely.

Keywords: Prophylactic salpingectomy, hysterectomy, ovarian reserve, AMH, doppler ultrasonography.

INTRODUCTION

Female life expectancy at birth is higher than male in all countries of the world (Mathers et al., 2001). The main reason for this statistical outcome is the ovarian sex hormones. Endogenous estrogen not only provide protection exclusively on cardiovascular diseases, osteoporosis and cognitive impairment but also improves the quality of life. On the other hand, ovarian cancer is a crucial entity which is the eighth most common cancer type with an incidence of 6.9 per 100.000 with the highest mortality in the developed countries and the second highest mortality including all countries in the world after cervical cancer (Ferlay et al., 2015). Several studies reported that most of the gynecologist were drafted to perform bilateral salpingo-oophorectomy during hysterectomy even in the pre-menopausal period which ranged from 37% to 78% (Asante et al., 2010, Whiteman et al., 2008, McAlpine et al., 2014). Oophorectomy would definitely decrease ovarian and breast cancer rates. However, it is not a riskless and innocent operation. Contemporary studies revealed that, bilateral

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oophorectomy especially before the age of 45 was related with an increased risk of mortality, cardiovascular disease, stroke, lung cancer, cognitive impairment, osteoporosis, fractures and impaired sexual function. Several authors have stated that bilateral oophorectomy could cause more harm than benefit (Parker, 2010, Parker, 2014, Parker et al., 2009).

To date, fallopian tubes are plausible origin of the high grade serous ovarian cancer which was initially exposed in patients harbor BRCA mutation (Piek et al., 2001). Subsequently, investigators exposed that tubal fimbria could be the origin of the serous ovarian carcinoma in patients who did not possess high risk and did not harbor BRCA mutation (Kindelberger et al., 2007, Reade et al., 2014, Liang et al., 2011). This theory was widely accepted and the term of prophylactic, elective or opportunistic salpingectomy was introduced which is one of the latest debates in gynecology. Some authors defended opportunistic salpingectomy due to the risk of the infection, torsion, prolapse, cancer, paratubal cysts and pelvic inflammatory disease (Repasy et al., 2009, Dietl et al., 2011). On the other hand, ovarian vascularity and the reserve were adversely affected after hysterectomy and salpingectomy might have diminished ever worsening (Siddle et al., 1987, Ahn et al., 2002). Recently; a systematic review stated that there was no sufficient evidence that opportunistic salpingectomy reduces the risk of ovarian cancer, however, they stated that prospective studies were missing in this subject (Darelius et al., 2017). We achieved a prospective randomized study that evaluate the effect of salpingectomy added to hysterectomy on ovarian reserve contribute to the literature on this missing subject.

MATERIALS AND METHODS

We designed a prospective randomized cohort study in Ege University Faculty of Medicine. Initially local ethic committee approval was obtained and the study was started in May 2014. Patients who were indicated hysterectomy with ovarian conservation for benign uterine indications, were included in the study aged less than 50. Each patient was enlightened about our study and informed consent form was obtained. Patients were randomized by using a computer-generated system of sealed envelopes to undergo either solely hysterectomy or hysterectomy and salpingectomy.

Patients were supposed to schedule three examinations including blood sampling for AMH evaluation and ultrasound scanning. The first examination was before operation, the second one was at the 6^{th} week of the operation and the last one was at the 6^{th} month of the operation.

Women were excluded from the study with age over 50, family history of ovarian or breast cancer, the presence of menopausal symptoms, history of adnexal operation, basal FSH value of >20 IU/mL, history of gonadotoxic medicine intervention, presence of ovarian pathology during operation and the patients who were not able to complete all three examinations. All patients were operated via laparotomy. Bilateral salpingectomy was performed as follows: Mesosalpinx was clamped with a succession of Kelly clamps as close to the Fallopian tube as possible. Mesosalpinx was closed with sutures without using electrosurgery. Care attention was performed to avoid ovarian vascularization impairment.

Biochemical Assay of AMH: All participants were evaluated preoperative and postoperative 6^{th} week and 6^{th} month in terms of AMH. Blood samples were obtained in a tube and left in a standing position for about 20-30 minutes at room temperature than centrifuged 10 minutes at 3000 RCF to obtain blood serum. These samples were stored in -80^0C deep freeze. After obtaining all samples, AMH evaluations were achieved by a physician who was blind to the study. Before AMH assay, plasma samples were taken out from -80^0C deep freeze and melted to room temperature and then centrifuged. AMH level of plasma samples were assayed with Gen II ELISA (Beckman Coulter Inc., CA, USA) commercial kit. In brief, calibrators, controls (low and high) and plasma samples were put in plates including 96 holes and covered anti-AMH antibody assay was performed with paired sample. After incubation and washing process, biotin was put in plate's hole as result of marked anti-AMH antibody. After the second incubation and washing process, stretaavidin-horseradish peroxidase (HRP) was put in plate's entire hole. After the third incubation and washing process substrate of tetramet ilbenzidin (TMB) was put. Reaction was terminated with added acidic solution after incubation of 15-20 minute. Degree of substrate's enzymatic change was determined 450 nm in micro-plaque assay. Measurement of absorbance was changing depending on concentration of AMH in samples. Levels of AMH were diagnosed according to calibration cure which was drawn with respect to absorbance of calibrator and represented with ng/mL. The lowest and highest levels of the AMH measurement kit was assayed between 0.16 and 22.5 ng/mL.

Ultrasound evaluation: All ultrasonography examinations were performed by the same physician who was blinded to study. Ovarian volume, AFC and ovarian stromal blood flow evaluation were performed by Voluson E8 Expert (GE Medical Systems) with 4-9MHz transvaginal transducer probe. Women underwent ultrasonography performance in the early follicular phase of the menstruation period. After hysterectomy, the early follicular phase was estimated due to the initial menstruation diary, relief of menstrual symptoms, lack of dominant follicle in ultrasound and the presence of serum progesterone level < 1 ng/mL.In ultrasonographic scan, follicles in 2-8mm diameter were counted as antral follicle

Table 1. The demographic and operational data of the patients.

	Group1	Group 2	P value
Number of patients	34 %54	29 %46	
Age (years)	42.4 ± 1.8 Range: 39-45	41.8 ± 2 Range:37-46	0.311
Body Mass Index (kg/m2)	Mean: 29.1±5.8 Median: 28	Mean: 28±4.4 Median: 28	0.516
Gravida	Median: 3	Median :3	0.828
Parity	Median:2	Median:2	0.772
Operative time min	Mean: 121± 24 95% CI: 112-129	Mean :117± 27 95% CI :107-128	0.467
Blood loss in operation (cc)	170 95% CI: 112-228	170 95%CI: 109-231	0.585
Complication(%)	0	0	

in each ovary. Ovarian volume was calculated by using 3 dimensional ultrasound technology. Each ovary was centered in the rectangular window including the all boundaries. Ultrasound machine had automatically swept the ovary by 30^0. Ovary's boundaries were manually drawn and automatically ovarian volume was obtained. Ovarian stromal blood flow was determined by color Doppler ultrasonography which was away from the capsule, follicle and utero-ovarian ligament. Peak systolic velocity(PSV), Pulsatility index (PI) were assessed by power Doppler ultrasonography. The calculation of PI is based on the following formulas: PI = (S − D)/mean, where 'S' is the peak systolic velocity, 'D' is the end diastolic velocity and the 'mean' is the averaged maximum velocity.

Statistical Analysis

Patients' demographic, operational data, pre-operative and post-operative AMH values, ultrasonographic data were recorded. Variables are described as frequencies, mean ± standard deviation of the mean, and median with ranges. The normal distribution of continuous variables was evaluated using the Shapiro-Wilk test. Patients' data were compared between groups and also within the group due to all three evaluations. Differences between and within groups were analyzed using Mann-Whitney and Wilcoxon tests and p value < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 21.0 software for Windows.

Ege University Faculty of Medicine local ethic committee approval was obtained on May 12th 2014 with an approval number of B.30.2.EGE.0.20.05.00/OY/579/288.

RESULTS

Patients were divided into two groups according to operation type. In group 1, patients underwent hysterectomy and opportunistic salpingectomy and in group 2 only hysterectomy was performed. All patients were operated by same operators and operations were performed via laparotomy. Seventy patients were eligible for our study, however;63 patients were able to complete all fallow up. Thirty-four patients were included in group 1 and 29 participants were included in group 2. Forty-five patients' ultrasonographic evaluations were able to be determined in all three controls. Rest of the patients' scanning were unable to be completed because of the difficulty in screening ovaries due to size of the uterus in pre-operative period and ovaries were unable to be seen in the post-operative time because of the obesity.

Patients were randomly separated into two groups, yet two groups were homogenous in demographic data and operational data. These data were compared between two groups and no statistically significant difference was detected. The demographic and operational data were shown in table 1.

Blood samples were obtained three times for AMH evaluation (pre-operative time: AMH 1, post-operative 6th week control: AMH 2 and post-operative 6th month: AMH3). These values were compared between groups to reveal the effect of opportunistic salpingectomy on ovarian reserve and values were compared within the groups to reveal the effect of the operation solely on ovarian reserve. AMH values were significantly decreased comparing pre-operative and post-operative values in both groups, however; when the groups were compared there was no statistically significant difference which were shown in Table 2 and 3.

Forty-five of 63 patients' ovaries were evaluated bilaterally and adequately three times by ultrasonography for ovarian reserve. AFC, ovarian volume and Doppler sonography (PSV, PI) were evaluated in right ovary (RO) and left ovary (LO). Mean values and the statistically comparison of the AFC and ovarian volume were shown in table 4.It is notable that ovarian volumes after hysterectomy were increased except left ovary in Group

Table 2. Comparison of AMH values between two groups.

	Group 1	Group 2	P value
Number of patients	34	29	
Mean AMH1	2.44 ng/mL	2.1 ng/mL	0.241
Mean AMH2	1.8 ng/mL	1.77 ng/mL	0.591
Mean AMH3	1.61 ng/mL	1.67 ng/mL	0.544

Table 3. Comparison of AMH values within the groups.

	Group 1; p value	Group 2;p value
AMH 1 & AMH 2	0.000	0.002
AMH 1 & AMH 3	0.000	0.000
AMH 2 & AMH 3	0.057	0.23

Table 4. Alteration in the ultrasonographic measured ovarian reserve at pre-operative (1), post-operative 6th week (2) and post-operative 6th month (3).

	Group 1	Group 2	P value
Number(n) of patients	27	18	
L.O. AFC 1 (n)	3.8	4.4	0.530
L.O. AFC 2(n)	4.4	3.8	0.277
L.O. AFC 3(n)	3.7	4.3	0.431
L.O. Volume 1 (cm^3)	14.1	7.1	0.100
L.O. Volume 2 (cm3)	11.8	6.94	0.424
L.O. Volume 3 (cm3)	10.3	9.3	0.458
R.O. AFC 1 (n)	3.7	3.9	0.897
R.O. AFC 2 (n)	3.3	4.5	0.263
R.O. AFC 3 (n)	4	4.4	0.731
R.O. Volume 1 (cm3)	6.2	7.2	0.737
R.O. Volume 2 (cm3)	10.1	11.3	0.242
R.O. Volume 3 (cm3)	9	10	0.935

1. However, these values did not differ statistically significant as shown in the table 5.

Doppler ultrasonographic evaluation was performed in both ovaries. Two parameters were scanned for both ovaries three times. Total of 12 parameters were compared between two groups and only 2 of them (L.O. PI 1 and 3) were significantly differed. Rest of the parameters did not differ statistically significant. In table 6, all the values were shown.

DISCUSSION

Hysterectomy is the second most frequently performed surgical procedure in women at reproductive age. Bilateral salpingo-oophorectomy is practiced in 37-78% of these operations due to prevention of subsequent development of ovarian cancer (Whiteman et al., 2008, Asante et al., 2010, McAlpine et al., 2014). In each year, 14.700 deaths occur because of ovarian cancer, however; 490.000 women die due to cardiovascular diseases, 48.000 women die within 1 year after hip fracture and stroke accounts for approximately 86.900 deaths (Parker et al., 2007, Kung et al., 2008). Endogenous sex steroids undoubtedly have a protective effect of these fatal diseases. Recent studies have investigated the effect of oophorectomy on survival. Jacoby et al. performed a prospective study with 7.6 year follow up including 26.000 women. They stated that oophorectomy decreased the incidence of cancer and no increment in the incidence of coronary heart disease, stroke and hip fracture. By the way, they stated that 323 healthy ovaries should be excised to preclude one ovary cancer (Jacoby et al., 2011). Parker et al. reported the long term outcomes and mortality in patients with oophorectomy and ovarian conservation with 24 year follow up including 29.300 women. Patients with oophorectomy had lower risk of ovary and breast cancer yet, they had higher rate of mortality, coronary heart disease and lung cancer. They also investigated the outcomes in patients younger than 50 year old. They notified women who underwent oophorectomy before the age of 50 had a higher risk of

Table 5. Comparison of the values of the ovarian reserve between the initial value and the post-operative 6th month value.

	Group 1; p value	Group 2;p value
L.O. AFC 1 & L.O. AFC 3	0.94	0.97
R.O. AFC 1 & R.O. AFC 3	0.29	0.15
L.O. volume 1 & L.O. volume 3	0.49	0.58
R.O. volume 1 & R.O. volume 3	0.28	0.21

Table 6. Doppler ultrasonographic values of both ovaries and comparison between groups. All data are expressed as mean. * remarks statistically significant values.

	Group 1	**Group 2**	**pvalue**
L.O. PSV 1	14.589	11.460	0.610
L.O. PSV 2	14.893	8.7816	0.089
L.O. PSV 3	12.078	13.142	0.215
L.O. PI 1	1.2	1.8	0.020 *
L.O. PI 2	0.98	0.81	0.379
L.O. PI 3	0.78	1.26	0.010 *
R.O. PSV 1	11	8.1	0.266
R.O. PSV 2	11.1	10.4	0.737
R.O. PSV 3	11,5	13,7	0.473
R.O. PI 1	0.91	1.11	0.319
R.O. PI 2	0.9	0.98	0.737
R.O. PI 3	0.81	0.93	0.509

coronary heart disease, stroke and lung cancer. The risk of all cause of death was significantly higher in these patients than patients whose ovaries were conserved at the time of surgery (Parker et al., 2009). One contemporary study revealed that prophylactic oophorectomy should not be performed before the age 45 because of the increased risk of mortality (Rocca et al., 2006). In other study, authors determined that ovaries continue secreting hormones that is beneficial for coronary arteries, bones and libido and should be conserved unless there is pathology (Parker et al., 2005). Our study did not have a long term follow up, but, it is obvious that endogenous sex steroids were beneficial for healthy survival.

In the early 2000s, gynecologist and oncologist held a new assumption that, fallopian tubes could be the origin of the serous ovarian cancer (Piek et al., 2001). Several studies have exposed investigating the effect of salpingectomy on ovarian reserve. Some authors stated that salpingectomy decreases the ovarian reserve. Nevertheless, others determined useless fallopian tubes are the potential risk for infection, torsion, prolapse or malignancy (Lin et al., 2013, Orvieto et al., 2011, Gelbaya et al., 2006, Surrey and Schoolcraft, 2001). However, this is a great debate whether it has adverse effect or not. In our study we aimed to determine the effect of salpingectomy on ovarian reserve in patients who underwent hysterectomy for benign indications.

Recently a systematic review has published semtinizing opportunistic salpingectomy and effect on ovarian cancer. Authors had declared that there were not sufficient data to evaluate the beneficial effect of opportunistic salpingectomy on reduction risk of ovarian cancer. However, they stated that randomized prospective studies on opportunistic salpingectomy is lacking because they could review only 11 studies and only 3 of them were dealed about the effect of salpingectomy on ovarian reserve(Darelius et al., 2017) . Our study is one of the unique one to stand in the breach of this subject. The strength of our study is being prospective, randomized study design and ovarian reserve is measured by not only AMH which is independent of the menstrual cycle but also ultrasonographic evaluation. The limitation of the study is the small number of patients included in the study. One of the reasons of the number of the patients is the type of the operation. We included women who underwent hysterectomy via laparotomy. Patients who were performed hysterectomy via laparoscopy were excluded from the study because of the potential risk of ischemia-reperfusion injury. However, this procedure can also performed via laparoscopic and even single site laparoendoscopic surgery and vaginal route (Scheib, 2017)(Antosh et al., 2017) . We evaluated that ovarian reserves were significantly decreased after hysterectomy. This occurs due to the various anastomosis between the uterus and the ovaries and the possible damages during and the post-operative time through the ovarian vessels. That is compatible with the literature (Atabekoğlu et al., 2012, Yuan et al., 2015, Wang et al., 2013). However, we determined that

opportunistic salpingectomy had no additional adverse effect on ovarian reserve comparing both groups. There are some studies investigating same parameters. Morelli et al. designed a retrospective study including 79 women in each group. They exposed that salpingectomy had no additional alteration to ovarian reserve. Although our study is including less patients, being in a prospective design and evaluating patients for three times ensures the reliability of our study more powerful (Morelli et al., 2013). In a prospective study including 12 patients in each group, Sezik et al. investigated the effect of salpingectomy added to hysterectomy on ovarian reserve. They also evaluated that salpingectomy had no additional impairment on ovarian reserve. The limitation of their study was the number of the patients and using FSH and Estradiol to measure ovarian reserve which is menstrual cycle dependent although they aimed to detect early follicular time due to serum progesterone values and ultrasonographic view (Sezik et al., 2007).

Falconer et al. achieved glorious population based cohort study including almost 6 million participants within 36 years. They investigated the effect of operations especially salpingectomy, sterilization, hysterectomy and hysterectomy plus bilateral oophorectomy on ovarian cancer. They observed statistically significant risk of reduction for ovarian cancer comparing salpingectomized and unexposed population. They suggest to perform salpingectomy solely or concomitantly with other benign operations to reduce ovarian cancer risk (Falconer et al., 2015).

We used AMH to evaluate ovarian reserve. To our knowledge, AMH is one of the most effective and also popular tests. One of the most priceless properties of this test is being independent of the menstrual cycle. We determined that AMH values were significantly decreased in both groups comparing the pre-operative and post-operative status. However, this decline cannot be related with salpingectomy due to comparison of AMH between groups. Findley et al. had also similar study like us. They used AMH to measure ovarian reserve and reported that salpingectomy did not affect adversely ovarian reserve like us(Findley et al., 2013). New researches are proceeding to resolve the connection between AMH values and menopause (Long et al., 2000, Masiakos et al., 1999). This would give important information about the adverse effects of the operations. This will also give chance to choose operative or conservative treatment modalities such diseases like myoma uteri, endometriosis, osteoporosis or cardio-vascular disease. We evaluated ovarian reserve by ultrasonography. Ultrasonography is feasible and cheap method. We aimed to determine the alteration between the initial situation and post-operative time. In our study we detected no significant difference between and within the groups. In a recent study, the authors stated that patients who had 4 or less AFC were twice as likely to have undergone menopause within 7 years compared with patients who had more AFC (Wellons et al., 2013).

We evaluated ovaries by three dimensional ultrasound (3D US). Although conventional 2D ultrasound is feasible, easy and valuable, 3D US depicts more accurate and sophisticated anatomy of the ovary. We performed 3D US and ascertained ovarian volumes were increased comparing pre-operative and post-operative measures whereas AMH levels decreased. Three of 4 volume measurements were increased comparing pre-operative and post-operative period. Increased ovarian volume after hysterectomy was not compatible with aforementioned similar studies like ours (Morelli et al., 2013, Sezik et al., 2007). However, Nahas et al. detected increment in volume and decline in PI values. They associated these findings regarding to increased blood flow after operation. Our findings also supported these findings. On the other hand, decreased ovarian reserve would be associated with uterus' paracrine effect or impairment of ovarian blood supply. Derksen et al. hypothesized that uterus would inhibit the follicle depletion. Removal of the uterus would accelerate follicular loss, suggesting a paracrine effect of the uterus, endometrium or both on ovarian function (Derksen et al., 1998). The other hypothesis was the decline in ovarian blood supply would cause depletion of ovarian reserve. Nonetheless despite we evaluated the possible increased ovarian blood supply. Thus ovarian blood flow and volume analysis should be investigated precisely.

Ovarian stromal blood evaluation was determined in our study. We evaluated PSV and PI. All parameters did not differ significantly comparing two groups which is compatible with the literature. There is not a consensus on the most valuable parameter which predicts the ovarian blood supply adequately. PI is one of the most frequently used parameter in studies, reflects inversely proportional to flow. Morelli et al. compared PSV values between groups(hysterectomy with salpingectomy and sole hysterectomy) and no significant difference was detected like our study (Morelli et al., 2013). Nahas et al. and Sezik et al. detected the decline in PI values comparing pre-operative and post-operative situation like our study which was related the increase in blood flow (Sezik et al., 2007, Nahás et al., 2005). To best our knowledge, contemporary studies are essential to expose the merit and usefulness of ovarian stromal blood flow investigations.

Recently, a unique review has published appraising the operative outcomes of opportunistic salpingectomy at the time of benign hysterectomy. They stated that only operative time had differed as 16 minutes longer in salpingectomy group which was 4 minutes in our study. The rest of the parameters as estimated blood loss, hospital stay, or intra-operative or post-operative complications which was also compatible with our study. And the authors has stated that in the future, prospective

randomized studies comparing opportunistic salpingectomy and nosalpingectomy might be unethical due to the benefit of opportunistic salpingectomy (Kho and Wechter, 2017). In our opinion, this statement should be absolutely promoted.

In conclusion; it is widely accepted that fallopian tubes could be the origin of high-grade serous carcinoma. Prophylactic oophorectomy should not be performed unless there is family history of ovarian carcinoma, breast carcinoma and hereditary tumor gene carriers. In our study, we ascertained that additional removal of the fallopian tubes did not cause additional ovarian reserve impairment. Nevertheless, rigorous studies are essential with including more patients and longer follow up. On the other hand, to clarify the etiology of ovarian cancer and the connection between ovarian cancer and fallopian tubes, population based clinical, genetic and molecular studies are definitely warranted.

Compliance with Ethical Standards

Deniz Şimşek declares that he has no conflict of interest.
Ali Akdemir declares that he has no conflict of interest.
Ahmet Mete Ergenoğlu declares that he has no conflict of interest.
Çağrı Güven declares that he has no conflict of interest.
DilekTaşkıran declares that she has no conflict of interest.
Ahmet Özgür Yeniel declares that he has no conflict of interest.
Serdar Özşener declares that he has no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional (Ege University Faculty of Medicine local ethic committee approval was obtained on May 12th 2014 with an approval number of B.30.2.EGE.0.20.05.00/OY/579/288.) research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Before the operation; informed consent was obtained from all individual participants included in the study.

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