A PROSPECTIVE OBSERVATIONAL STUDY OF THE CLINICOPATHOLOGICAL PROFILE, EPIDEMIOLOGICAL RISK FACTORS AND FALLOPIAN TUBE MUCOSAL INVOLVEMENT IN OVARIAN CANCER

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ABSTRACT

BACKGROUND

Many of the ovarian tumours traditionally thought to be of ovarian origin is now thought to primarily originate in other pelvic organs and ovarian involvement is actually secondary.

MATERIALS AND METHODS

A prospective observational study was conducted in the Department of Obstetrics and Gynaecology, Government Medical College, Kozhikode, over a period of 10 months from January 2013 to October 2013. All cases of carcinoma ovary operated and specimen submitted for histopathology examination with no gross involvement of fallopian tubes were included in the study. All cases where specimen showed gross involvement of fallopian tubes or adherence of the fallopian tubes to the ovary were excluded. Bilateral salpingectomy specimens from women undergoing surgery for reasons other than ovarian, tubal or peritoneal malignancy were taken as controls. General information regarding the patients was collected. Investigation results were analysed. Histopathology examination of the specimen was done. Fallopian tube was examined by SEE-FIM (sectioning and extensive examination of fimbrial end) protocol and was submitted for p53 and Ki67 studies.

RESULTS

Pain was the most common presenting symptom. Ultrasound was suggestive of ovarian malignancy in majority. Tubal involvement was noted in 35% cases and 27% controls. 61% of cases were above 45 years of age. 60% of cases had not undergone tubal ligation. Family history of malignancy was more among cases.

CONCLUSION

Fallopian tube mucosal involvement was noted in 35% of cases and 30% of controls. These lesions can be considered as precursor lesions in carcinoma ovary. However, further studies with larger sample size is needed. Tubal ligation not done was found to be a significant risk factor for ovarian carcinoma. Age of menopause above 48 years and family history of malignancy were associated with increased risks. Incidence of ovarian carcinoma showed an increase with increasing age.

KEYWORDS

Ovarian Cancer, Fallopian Tube Mucosal Involvement, P53 Signature, Serous Tubal Intraepithelial Carcinoma.

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BACKGROUND

Worldwide ovarian cancer is the sixth most common malignancy diagnosed in women, the seventh leading cause of death from cancer in women and the leading cause of death among gynaecologic cancers.[1] Ovarian cancer is the third leading site of cancer among women in India, trailing behind cervix and breast.[2] Approximately, 75% of all ovarian cancers are in an advanced stage at the time of diagnosis thereby increasing the mortality and morbidity.

Approximately, 90% of malignant ovarian tumours in adults are of epithelial origin followed by sex cord-stromal tumours (6%) and germ cell tumours (3%). Epithelial ovarian tumours can be classified according to morphologic and molecular genetic features into two groups- type I tumours and type II tumours.[3] Type I tumours are composed of low-grade serous, low-grade endometrioid, clear cell, mucinous and transitional carcinomas. These tumours behave in an indolent fashion and are confined to the ovary at presentation. They lack mutations of TP53, but each histological type exhibits a distinct molecular genetic profile. In contrast, type II tumours are highly aggressive, evolve rapidly and are in an advanced stage at presentation. This constitutes about 75% of advanced ovarian cancers. Type II tumours include conventional high-grade serous carcinoma, undifferentiated carcinoma and malignant mixed

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mesodermal tumours. They display TP53 mutations in over 80% of cases.

Recent studies have provided evidence that many of the ovarian tumours traditionally thought to be of ovarian origin, primarily originate in other pelvic organs and ovarian involvement is actually secondary.[3] Thus, it has been proposed that serous tumours arise from the implantation of epithelium from the fallopian tube. It is well known that prophylactic salpingo-oophorectomy reduces the risk of carcinoma breast and ovary. Putative precursor lesions have been identified in the fallopian tube that morphologically and molecularly resembles high-grade ovarian serous carcinomas and are designated Serous Intraepithelial Tubal Carcinoma (STIC). Majority of type II tumours arise from a STIC in the fimbriated end of the fallopian tube.

Ovarian conservation appears to be particularly important for a woman's health as it is known that oophorectomy is associated with increased overall mortality and a higher frequency of nonfatal coronary heart disease. If it is proved that carcinoma ovary arises from a precursor lesion in fallopian tube, then salpingectomy alone may suffice to reduce the risk of ovarian cancer.

The relevance of this study is to gain an understanding on the fallopian tubal origin of ovarian cancer thereby providing a fresh outlook into the effective prevention of ovarian cancer.

AIMS

1. To explore the relationship between ovarian cancers and fallopian tube mucosal involvement.
2. To study the clinicopathologic profile and epidemiological risk factors in ovarian cancer.

MATERIALS AND METHODS

This was a prospective observational study conducted in the Department of Obstetrics and Gynaecology, Government Medical College, Kozhikode, over a period of 10 months from January 2013 to October 2013. All cases of carcinoma ovary operated and specimen submitted for histopathology examination with no gross involvement of fallopian tubes were included in the study. All cases where specimen showed gross involvement of fallopian tubes or adherence of the fallopian tubes to the ovary were excluded. Bilateral salpingectomy specimens from women undergoing surgery for reasons other than ovarian, tubal or peritoneal malignancy were taken as control.

General information regarding the patient was collected based on a preformed proforma. Detailed menstrual, obstetric and family history and associated risk factors were obtained. Investigation results were analysed. Intraoperative findings were noted. Histopathology examination of the specimen was done by the pathology department of the institution. Fallopian tubes were examined by SEE-FIM (Sectioning and Extensive Examination of Fimbrial end) protocol. All available sections were submitted for p53 and Ki-studies using standard techniques. Fallopian tube mucosal involvement in the form of atypia, p53 signatures and Serous Tubal Intraepithelial Carcinoma (STIC) were studied.

The study was approved by the Institutional Research Committee and Institutional Ethics Committee. Data entry was done in Microsoft Excel programme. Statistical analysis was done using SPSS version 16.0 for Windows. Qualitative data was expressed as frequency and percentages and quantitative data as mean or median with standard deviation. Data analysis was done by chi-square test and Fisher's exact test. Risk was calculated in terms of odds ratio (OR) and a 95% confidence interval for the risk was also estimated. A p value <0.05 was considered to indicate statistical significance.

OBSERVATIONS AND RESULTS

26 cases of carcinoma ovary with grossly normal fallopian tubes were taken up for the study. Clinicopathologic profile and epidemiologic risk factors were studied in these patients. 26 patients who underwent surgery for reasons other than ovarian, tubal or peritoneal malignancy were taken as control. Epidemiological risk factors and pathologic profile were studied in controls. Fallopian tube involvement in both groups were studied by SEE-FM protocol. Prevalence of risk factors in both groups were analysed.

Clinicopathologic Profile

Abdominal pain was the most common presenting symptom in 73% of cases as depicted in Figure 1. Next common symptom was feeling of abdominal distension, which was present in 46% of cases. Mass was detected by abdominal or per vaginal examination in 80% (21/26) of cases. Among them, mass was cystic in 71%, solid in 5% and varying in consistency in 24%. Ascites was detected in 8% of cases. Either transabdominal or transvaginal sonography was done in all patients. Size, echogenicity or presence of solid particles, septations and presence of ascites were noted. Mass was detected in 96% (25/26) of cases. The size of the mass varied from less than 10 cms to more than 20 cms. Ascites was noted in 23% (6/26). Ultrasound findings were supportive of malignant ovarian neoplasm in 92% of cases as shown in Figure 2. Number of sonologically detected ascites was more than by clinical examination. Doppler examination was done in 6 cases. 5 of them showed evidence of increased vascularity. CT scan was done in 22 cases. 86% of them showed features suggestive of malignancy. Heterogenous or mixed density lesions with internal septations, solid areas with or without ascites were noted. Infiltration to adjacent areas were noted in some cases. CA125 was done in all cases. There was a rise of CA125 in 21 of the 26 cases (81%). The range varied from 4.5 to 3009. CA125 was less than 35 in 5 cases.

Pathologic Profile

The changes in fallopian tube included atypia, p53 signatures and STIC. p53 signatures were noted in 3 cases and 3 controls (12%) as shown in Figure 3. Fallopian tubes showed atypia in 6 cases of which p53 positivity that is STIC was noted in 4 cases. Among controls, 4 showed atypia of

which 3 showed p53 positivity. STIC was noted in 4 cases (15%) and 3 controls (12%) as seen in Figure 4. Atypia alone was noted in 2 cases and 1 control. Any form of tubal involvement was noted in 9 cases (35%) and 7 controls (30%), which is shown in Figure 5.

Epidemiological Risk Factors

Age group of cases ranged between 23 to 60 years. Figure 6 shows the age distribution of the cases. 61% of cases were above 45 years. Age at menarche ranged from 12 to 16 years in cases and 13 to 18 years in controls and is shown in Table 1. Mean age at menarche for cases (14.12) and controls (14) were almost similar. Table 2 shows the menopausal status of the study group. 46% (12/26) of cases and 12% (3/26) of controls had attained menopause. Mean age of menopause was 49.6 among cases, which was more than the mean age of controls, which was 47.6. The difference is statistically significant. 2 women from both groups had treatment with clomiphene citrate. The difference is not statistically significant. Parity in cases and controls is shown in Table 3. 1 woman from control and 2 women from cases were unmarried and hence excluded. Parity of 1 or less was not found to be significant risk factor for ovarian malignancy. 60% of cases had not undergone tubal ligation, whereas 46% of controls had undergone tubal sterilisation as seen in Table 4. Tubal ligation not done was found to be a significant risk factor for ovarian malignancy. Only 2 among controls used OCP. None in cases or controls used HRT. History of PCOD was present in 1 patient among the control group. Positive family history of malignancy (breast, colon, ovary, endometrium) was present among 23% of cases and 4% of controls and is depicted in Figure 7. Though, this was not statistically significant, those with family history of malignancy were more among cases. Practice of perineal use of talc was not seen in cases or controls. 96% of cases and controls had normal BMI. 2 of the cases were malnourished. None had BMI more than 25.

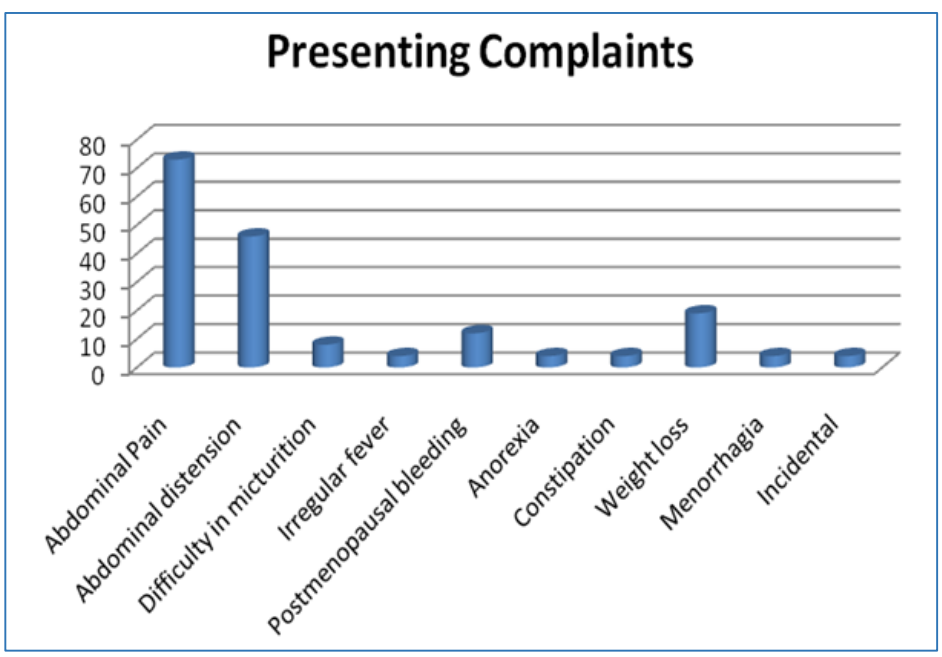

Figure 1. Presenting Complaints

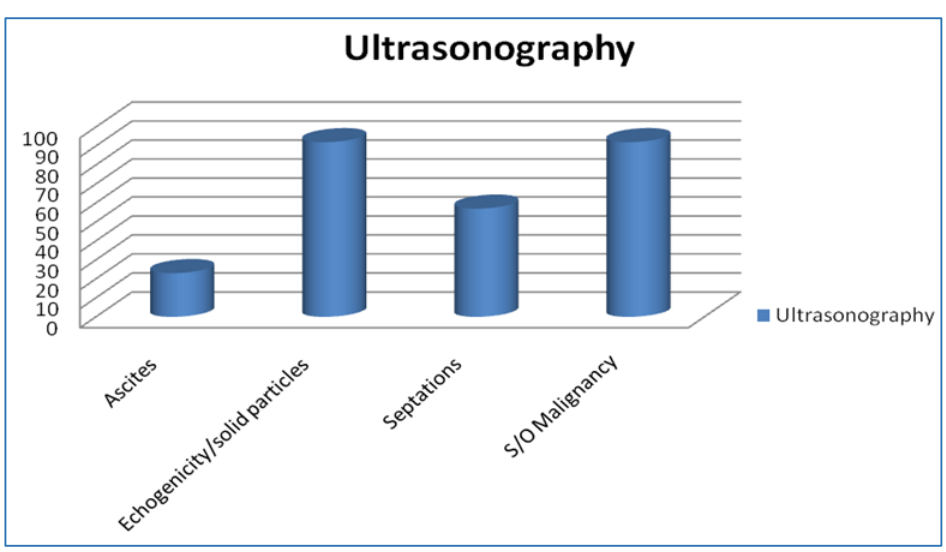

Figure 2. Ultrasound Findings

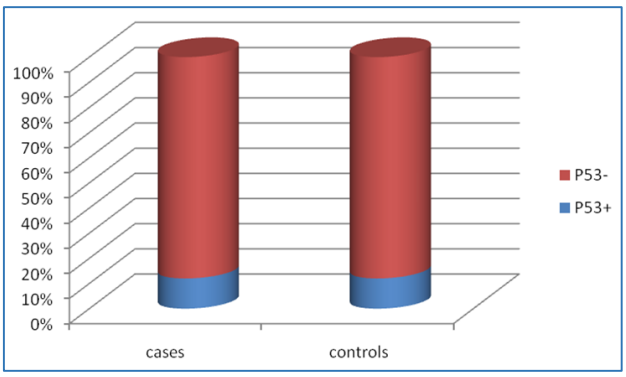

Figure 3. p53 Signature

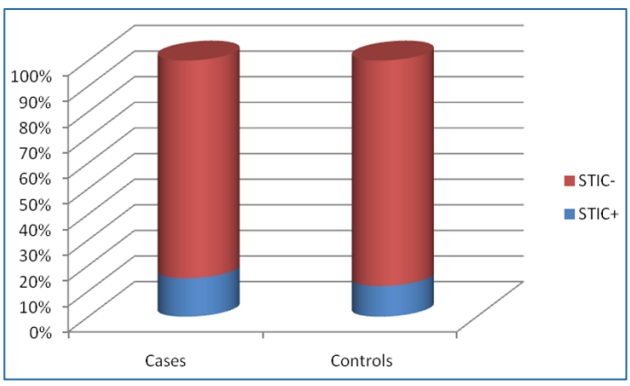

Figure 4. Serous Tubal Intraepithelial Carcinoma (STIC)

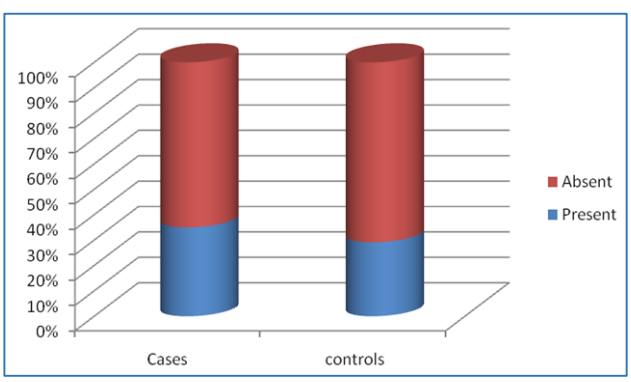

Figure 5. Tubal Involvement

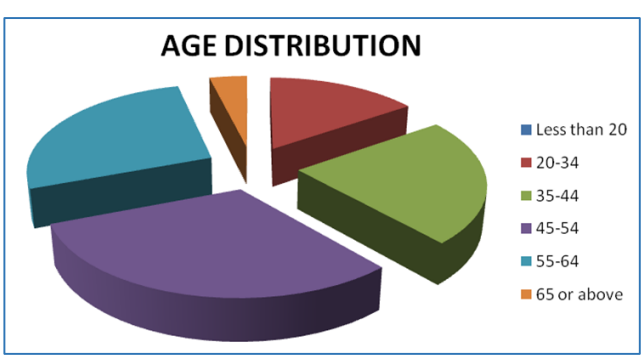

Figure 6. Age Distribution

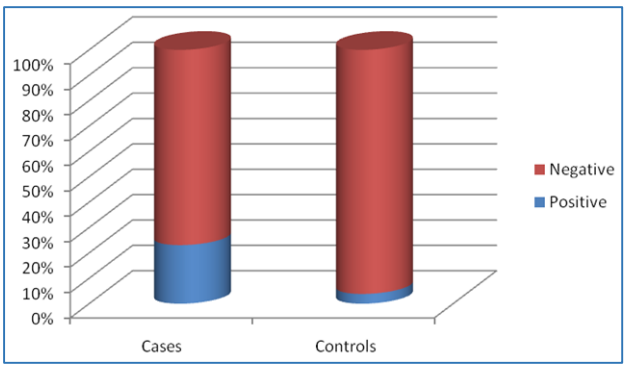

Figure 7. Family History of Malignancy

Age (Years)	Cases (N=26)	Controls (N=26)
12	1	0
13	8	12
14	7	10
15	7	0
16	3	1
17	0	2
18	0	1
	Mean Age - 14.2	Mean Age - 14

Table 1. Age at Menarche

Menopausal Status	Cases (N=26)	Controls (N=26)
Postmenopausal	13	3
Premenopausal	13	23
Mean age	49.6	47.6

Table 2. Menopausal Status

Parity	Cases (N=26)	Controls (N=26)
0	1	2
1	3	2
2	7	14
3	8	5
4	1	1
5 or more	4	1
Unmarried	2	1

Table 3. Parity

OR=0.54 95% CI (0.14-2.09) p=0.315

Tubal Ligation	Cases (N=26)	Controls (N=26)
Not done	21 (60%)	14 (54%)
Done	5 (29%)	12 (46%)

Table 4.Tubal Ligation in Cases and Controls

OR=3.6, 95% CI (0.9-15.17) p=0.039

DISCUSSION

Most ovarian tumours (96%) are epithelial in origin. These are rare before 35 years, but the incidence increases with age to a peak in the 50-70 year old age group.[4] In the present study, 96% of ovarian malignancies belong to surface epithelial tumours. 71% of surface epithelial

tumours were serous cystadenomas followed by mucinous variety. No germ cell tumours were reported.

Tumour may remain symptomless in 15% of patients.[5] 96% of patients in this study presented with symptoms. Most common symptom was abdominal pain (73%) followed by feeling of abdominal distension. The use of ultrasound as a screening tool of ovarian cancer was suggested in 1989 by Campbell et al. Morphologic features that seem to correlate with malignancy include papillary excrescences, thick and irregular septae or wall, internal echogenicity, presence of ascites and characteristics of mass.[6] In the present study, any one of these findings suggestive of malignancy was found in 92% of patients. CA125 was done in all cases. 81% of the cases showed elevated CA125 levels.

In the present study, fallopian tube involvement was noted in 35% of cases and 30% of controls. p53 signatures were noted in 12% of cases and 12% of controls. STIC was present in 15% of cases and 12% of controls. This study provides evidence to the presence of precursor lesions in the fallopian tubes. Since, the cases and controls have shown intraepithelial precursor lesions, this may represent the continuum of changes as we do not know the temporal relationship between the inciting pathogenic event and development of these lesions.

Putting these statements in a positive sense, 9/26 (35%) of cases showed fallopian tube mucosal changes. The changes are non-contiguous from the ovarian tumour. These lesions can be argued as metastatic lesions, but such non-contiguous focal metastatic lesions are rare. Moreover, previous studies have identified similar lesions in pelvic serous carcinoma in approximately 50% of cases. Analysis of TP53 mutations in these lesions and adjacent carcinomas showed shared mutations suggesting a clonal relationship between them.[7] This gives a strong evidence that carcinoma ovary develops from precursor lesions in fallopian tube.

7/26 (30%) of controls showed fallopian tube changes in the form of atypia, p53 signatures and STIC. BRCA status of these patients is unknown. The histopathological examination of their ovaries did not reveal any invasive carcinoma. Previous studies have shown similar lesions in risk reducing bilateral salpingo-oophorectomy specimen of healthy women in distal fallopian tubes.[7] The finding of precursor lesions in the controls was unexpected. This strongly suggests that these lesions can be the precursor lesions in ovarian carcinoma. So, the hypothesis that fallopian tube is the site of origin of ovarian carcinoma becomes important.

Patricia Martini et al of Brazil observed fallopian tube involvement in 24/34 (70.6%) cases.[8] In 4 (11.8%) of these cases, an intraepithelial neoplasia was present, and therefore, these cases were hypothesised to be primary from fallopian tubes. For an additional 7/34 (20.6%) cases, a fallopian tube origin was considered a possible primary.

The association of risk factors were analysed in the present study. Data from office of population of census and surveys (1981) showed an increased incidence of ovarian cancer with age up to sixth decade. This study also shows a rise in the incidence after 45 years. But, the number of cases above 65 years is less probably because some of the older patients were treated with radiation and hence not included.

Berol et al described high risk of developing ovarian malignancy with decrease in family size.[9] They point out that pregnancy would seem to be protective whether ending in abortion or not. In the present study, small family of one or less was not found to be a risk factor (p=0.31), not statistically significant.

Early menarche and late menopause are associated with increased risk. Prolonged period of ovulation results in malignancy.[10] In the present study, mean age of menarche was similar in cases (14.1) and controls (14). Age of menarche 13 years or less was found to be a significant risk factor for ovarian malignancy in previous studies. Mean age of menopause among cases was 49.6 years when compared to controls (47.6). Age of menopause above 49 years (OR=2.13; 95% CI=0.56-8.19; p=0.265) was found to be a risk factor, but not statistically significant.

There has been reports of reduced risk of ovarian cancer due to the practice of tubal sterilisation.[11,12] It appears that the association between tubectomy and ovarian cancer is biologically possible since tubal ligation could act as a physical barrier to prevent the passage of carcinogen. Neil et al have shown that tubectomy could decrease the vascular supply to ovaries that could reduce the risk of ovarian cancer.[13] In the present study, 80% of cases had not undergone tubal ligation, whereas 46% of the controls had undergone tubal sterilisation. Tubal ligation not done was found to be a significant risk factor for ovarian malignancy (p=0.039).

Family history of any type of malignancy, which was considered as risk factor in many studies was seen in 23% of cases and 4% of controls.[14,15] Family history of malignancy was more among cases. So, this could be a possible risk factor as we do not know the BRCA status, but this was not statistically significant.

Other risk factors found to have a role in ovarian malignancy were perineal use of talc and hormone replacement therapy. Two published meta-analyses produced conflicting results. The earlier analysis of 10 studies indicated a small, but statistically significant increase in risk in ever versus never users of HRT.[16] A more recent analysis of 15 case control studies concluded that there was no significant association between ever and never use nor any evident dose response relationship.[17] Studies show a statistically significant increased risk associated with talc use. None of the risk factors mentioned above were present in our patients.

Case control studies done in Australia showed that women with a body mass index above 85th percentile had approximately double the risk of ovarian cancer than women in the middle 30% of BMI range.[18] The International Agency for Research in Cancer was unable to draw a conclusion on possible association between BMI and ovarian cancer. In our study, 96% of cases and controls had normal BMI. 2 of the cases were malnourished. None had BMI more than 25. This maybe because study population was mainly from poor socioeconomic status and late stage of presentation.

CONCLUSION

The hypothesis that fallopian tube mucosal involvement occurs as precursor lesions in ovarian carcinoma is significant and needs further extensive studies. Clinical presentation and usefulness of investigative modalities of primary ovarian malignancies are comparable with other studies. Tubal ligation not done was found to be a definite risk factor. Age of menopause above 48 years and positive family history are associated with increased risks. Age at menarche and low parity are not identified as risk factors. The relationship of malignancy rates to other proposed risk factors like OCP, HRT, PCOS, obesity, infertility treatment and perineal use of talc are inconclusive. These risk factors, which were not present in our study population have to be studied with a larger sample.

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