EVALUATION OF SEE-FIM (SECTIONING AND EXTENSIVELY EXAMINING THE FIMBRIATED END) PROTOCOL IN IDENTIFYING FALLOPIAN TUBE PRECURSOR LESIONS IN WOMEN WITH OVARIAN TUMORS.

By

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Dissertation submitted to the

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In partial fulfillment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

PATHOLOGY

Under the Guidance of

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ABSTRACT

BACKGROUND

Ovarian tumors are one of the lethal gynecological cancers. They are usually diagnosed at advanced stages and the screening tools are also not effective for early detection. Studies of prophylactic salpingo-oophorectomies in high risk population led to the incidental finding of precursor lesions in the fimbrial end of fallopian tube rather than the ovary. Early detection of these precursor lesions can be helpful in prevention of ovarian tumors and the presence of these lesions in fimbria can be more efficiently studied by applying SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) protocol as it maximizes the area under evaluation.

OBJECTIVE

To study histological findings of fallopian tubes associated with ovarian tumors by applying SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) protocol.

MATERIAL AND METHODS

Specimens of hysterectomy with bilateral salpingo-oophorectomy having clinical diagnosis of ovarian tumor received during last 1 year and 8 months from 1st November 2013 to 30th June 2015 were examined by SEE-FIM protocol, which includes serial longitudinal sections of the fimbriated end and transverse sections of rest of the tube . Histological changes in fallopian tube were grouped either as Tubal Intraepithelial Carcinoma (TIC), Tubal Intraepithelial Lesion (TIL), only stratification and negative for any changes. Specimens without ovarian tumor were taken as control group and same protocol was applied on them.

RESULTS

Out of 60 cases of ovarian tumors, 19 (31.67%) cases showed changes of TIC in fallopian tubes, 10(16.67%) revealed TIL, 14 cases (23.33%) showed changes of stratification and 17 (28.33%) were negative for any changes in the tubes. Among the 60 cases, there were 7 cases of High Grade Serous Carcinoma (HGSC), 5 cases (71.43%) showed changes of TIC in the tubes and rest 2 showed TIL.

In the control group, out of 60 cases none of the cases showed changes of TIC in fallopian tube, TIL was noted in 4 (6.66%) cases. 16 cases (26.67%) showed changes of stratification and 40 (66.67%) were negative for any changes in the tubes.

CONCLUSION

SEE-FIM protocol maximizes the examination of fimbrial end and is helpful in identifying precursor lesions that could be useful for early detection and prevention of ovarian carcinomas.

KEYWORDS – SEE-FIM protocol, Ovarian tumors, TIC.

LIST OF ABBREVIATIONS USED

SEE-FIM	Sectioning and Extensively Examining the FIMbriated end
TIC	Tubal Intraepithelial Carcinoma
TIL	Tubal Intraepithelial Lesion
HGSC	High Grade Serous Carcinoma
EOC	Epithelial Ovarian Carcinoma
FIGO	Federation of Obstetrics and Gynecology
LGSC	Low Grade Serous Carcinoma
APST	Atypical Proliferative Serous Tumor
MPSC	Micropapillary Serous Carcinoma
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
HRT	Hormone Replacement Therapy
NA-NSAIDs	Non aspirin – Non steroidal anti- inflammatory drugs
PLCO	Prostate, Lung, Colorectal and Ovarian
BSO	Bilateral Salpingo-Oophorectomy
CIC	Cortical inclusion cysts
FTE	Fallopian Tube Epithelium
OSE	Ovarian Surface Epithelium
STIC	Serous Tubal Intraepithelial Carcinoma
CCC	Clear Cell Carcinoma
EC	Endometrioid Carcinoma
LOH	Loss of Heterozygosity
OCAC	Ovarian Cancer Association Consortium
IHC	Immunohistochemistry
STIL	Serous Tubal Intraepithelial Lesion
BPSO	Bilateral Prophylactic Salpingo-Oophorectomy
RRSO	Risk Reducing Salpingo-Oophorectomy
H&E	Haematoxylin and Eosin
x	Magnification

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INTRODUCTION

Ovarian cancer is one of the leading cause of death due to gynecologic malignancies and the fifth most common cause of cancer deaths in women. 5-year survival rate is greater than 95% for stage I tumors, in contrast to 15 - 30% for advanced stage disease with spread beyond the ovary (stage III/IV).[1]

Unfortunately, the majority of women with ovarian cancer, including those with the most common subtype High Grade Serous Carcinoma (HGSC), are diagnosed at an advanced stage. This could be attributed to lack of effective screening tools for early detection of ovarian cancer in high risk and general populations.[2]

Serous carcinomas are the most lethal form of pelvic epithelial cancers due to their propensity for serosal organ involvement and rapid peritoneal spread. Studies of prophylactic salpingo – oophorectomies in women with BRCA1/2 have identified the fallopian tube as a source of early serous carcinoma.[3]

This study is done to know the histological changes in fallopian tubes associated with ovarian tumors by applying SEE-FIM (Sectioning and Extensively Examining the FIMbriated end) protocol and thus aims at identification of precursor lesions that could be useful for early detection and prevention of these carcinomas.

OBJECTIVE OF THE STUDY

To study histological findings of fallopian tubes associated with ovarian tumors by applying SEE-FIM protocol.

REVIEW OF LITERATURE

2.1 OVARIAN CARCINOMA

Although ovarian carcinoma accounts only for 3% of all cancer diagnoses, it is the fourth leading cause of cancer deaths amongst women aged 40-50 and the fifth leading cause amongst women of all ages.[4]

Epithelial Ovarian Carcinoma (EOC) is the most common type of ovarian carcinoma and has the most unfavorable prognosis amongst the gynecological diseases, with an overall mortality of 65% within the first 5 years of diagnosis.[5] However, the five year survival rate largely depends on disease progression at the time of presentation, where early stage detection leads to an overall survival of 80% while late stage detection leads to an overall survival of just 15%.[5] Unfortunately ovarian cancers are only identified at early stages in about 20% of the cases.[6] Additional to the late stage diagnosis of ovarian carcinoma, another contributing factor to poor prognosis is a lack of effective treatment options.

Currently, the primary treatment of choice is radical surgical resection of these tumors, including bilateral salpingo-oophorectomy, hysterectomy, omentectomy as well as additional individualized resections depending on the extent of the disease within and outside the peritoneal cavity.[5] The surgery is followed by platinum and/or taxane based chemotherapy treatments, administered either by intra-venous or intra-peritoneal methods and responses to these treatments are variable.[5]

2.1.1 Histotypes

Epithelial Ovarian Carcinomas (EOCs) are the most common subgroup of ovarian cancer and represent a heterogeneous group of neoplasms, which pathologists have classified based on histological and morphological features. Four of the most common histotypes are the serous, clear cell, endometrioid and mucinous ovarian

carcinomas. The serous cancers show the highest incidence at a frequency of 68-71%, while clear cell tumors have a prevalence of 12-13%, endometrioid cancers make up only 9-11% of all EOCs, and mucinous tumors are the least prevalent at a frequency of 3%.[7] This histological classification has proven to be the most important prognostic factor in the ovarian carcinoma field.[7]

Staging

In addition to the histological classification, ovarian tumors have also been characterized by grade and stage. Tumor grading in pathology represents a measure of cellular appearance, while tumor staging represents a measure of the extent to which the tumor has spread. Epithelial Ovarian Tumors are staged at the time of surgery, based on the Federation of Gynecology and Obstetrics (FIGO) classification method, in order to have a measurement of how far the cancer has spread.[8] Staging also represents a very accurate predictor of prognosis. Stage I identifies ovarian tumors that are confined to one or both ovaries and may be present on the surface of this organ, while stage II represents disease that has spread from the ovaries but remains confined to the pelvis and does not extend to the abdomen.[9] Organs that may be affected at stage II include fallopian tubes, uterus, rectum and bladder. Stage III is the most commonly diagnosed group of tumors and is represented by the spread of the tumor to the upper abdominal regions such as peritoneum, omentum and diaphragm, and/or to lymph nodes.[9] Stage IV is the most advanced stage and represents metastasis of the tumor outside the abdominal cavity, and/or to the parenchyma of other organs such as liver and lungs.[9]

Staging of tumors remains closely linked to the ovarian cancer histotype, as it is recognized that most serous ovarian tumors are diagnosed at late stages, while other

histological subtypes such as endometrioid and clear cell tumors are more commonly detected at earlier stages.[8,9]

Grading

Grading represents an additional classification methodology for EOC, routinely performed by pathologists. There are several commonly used systems such as the International FIGO grading system, the Gynecologic Oncology Group (GOG) system and the three tiered Shimizu Silverberg grading system.[8] The FIGO system takes into consideration architectural features, where lower scores are assigned to tumors with a glandular or papillary structures and higher scores are assigned to cases with solid tumor growth, but different grading systems are applied dependent on the histotype.[10] The Silverberg system is similar to the Nottingham system for grading breast cancer tumors and includes an objective score of all histotypes based on architectural, nuclear and mitotic features .[11,12]

A more recent system was devised by a group at M.D. Anderson termed the two-tier grading system, which is applied only to the serous ovarian carcinomas and is based on the analysis of nuclear atypia and mitotic rate.[12] It is an easily reproducible and clinically meaningful system that essentially categorizes the Silverberg grade I tumors as low grade and the Silverberg grade II and III tumors as high grade.[12] Low grade serous tumors are defined by mild to moderate nuclear atypia, while high grade serous tumors show high nuclear atypia and more than 12 mitosis per 10 high power fields.[12] This system lead to the classification of these tumors into two clinically meaningful subgroups termed Low Grade Serous Carcinoma (LGSC) and High Grade Serous Carcinoma (HGSC), which are now believed to represent completely separate disease entities and which are recognized by the World Health Organization as independent categories.

2.1.2 LGSC and HGSC

A dualistic model of ovarian carcinogenesis had been proposed, based on the morphologic, molecular and immunohistochemical features. It had classified ovarian carcinomas into two groups (Figure 1) namely, Type I and Type II. [2,13]

Type I includes – LGSC, Low Grade Endometrioid carcinomas, Clear cell and Mucinous carcinomas and Brenner tumors.[2,13]

Type II includes – HGSC, High Grade Endometrioid carcinomas, Malignant mixed mesodermal tumors and Undifferentiated carcinomas.[2,13]

Type I tumors typically affect women between the age of 40 and 50 and are slow-growing. They are also chemo-resistant to platinum-based drug regimens. Type 1 tumors have well-established precursor lesions that can be histologically and molecularly identified in this disease and also illustrate their slow development. Clinicopathologic studies have identified a benign non-invasive borderline tumor characterized by a hierarchical branching pattern, which represents the first precursor lesion towards the development of LGSC and is classified as “atypical proliferative serous tumor” (APST).[14,15]

A second noninvasive precursor lesion is a “micropapillary serous carcinoma” (MPSC), which maintains micropapillary pattern but has lost the hierarchical branching.[16] Although initially non-invasive, this lesion is thought to be the immediate precursor of LGSC.[16]

The LGSC is characterized histologically by small solid nests and micropapillae.[16] Molecular characterization of Type I category (Figure 1) identifies these tumors as genetically stable but harbouring specific mutations in KRAS, BRAF, ERBB2, PTEN, PIK3CA and CTNNB1 (gene encoding beta Catenin) .[14,17,18]

In contrast, Type II tumors (mainly HGSC) have a poorly differentiated morphology with high nuclear/cytoplasmic ratio, high mitotic index and marked pleomorphism.[19] They also have a highly aggressive and proliferative nature and up until recently were believed to spontaneously arise de-novo in the ovaries in the absence of a reproducible histological cancer precursor. Molecularly these tumors are highly heterogeneous with only a few defining common features. The most common genomic alteration is that of p53 mutations, identified in 97% of HGSC, which represents the highest mutation frequency amongst solid tumors.[20-22] This seems to be a unique feature of HGSC, as other solid tumors rely on additional p53 pathway alterations for pathogenesis, such as functional inactivation of MDM2, the protein known to target p53 for degradation.[20] A second defining feature of all tumors is the high level of genomic instability, represented by large spanning amplifications and deletions.[22] Clinically, patients with HGSC also show heterogeneity in their response to treatment, as some show high sensitivity to primary platinum based chemotherapy, while others show primary or partial chemoresistance.[23,24]

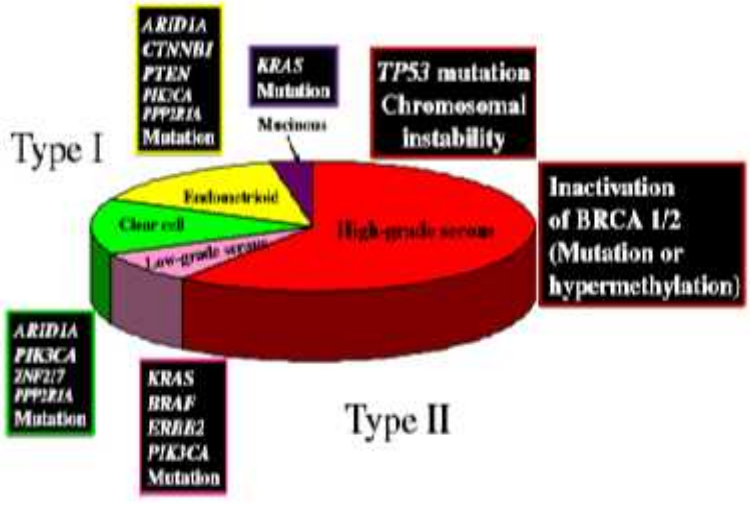

Figure 1: Histotypes of Epithelial Ovarian Carcinoma (EOC) and their associated molecular alterations.[13]

2. 1.3. Risk Factors

Germline mutations

Western countries such as Europe, Canada and US show the highest rates of ovarian cancer, especially HGSC.[4] Family history is the strongest risk factor for ovarian cancer development due to genetic predispositions associated with highly penetrant, autosomal dominant germline mutations .[25]

Currently, it is accepted that 10-15% of ovarian cancers are hereditary and that 90% of the time they are attributed to mutations in BRCA genes, while an additional 1-2% are attributed to hereditary nonpolyposis colorectal cancer (HNPCC), associated with germ line mutations in the DNA mismatch repair (MMR) genes, such as hMLH1 and hMSH2.[25-28] BRCA1 and BRCA2 mutations confer a skewed increased lifetime risk for ovarian cancer, with 50-60% attributed to BRCA1 mutations and a risk of 18 - 23% attributed to BRCA2 mutations, compared to a much lower risk of 1.6% identified in the general population.[29] Interestingly, 98% of BRCA1/2 mutation carriers develop the HGSC subtype of ovarian cancer .[26]

Ovulation

Several additional epidemiologic risk factors have been identified and many of them are linked to the effects of ovulation and the menstrual cycle. Lifetime ovulation events are a well known risk factor .[30]

Breastfeeding, oral contraceptives, increased parity and tubal ligation have been associated with a decreased risk of ovarian cancer.[31,32]

Other factors which affect risk of ovarian cancer are; lifestyle factors such as cigarette smoking, obesity, diet and exposure to certain environmental agents such as talc, pesticides and herbicides.[32]

Additionally, analysis of fallopian tube epithelium from BRCA1/2 mutation carriers for non-invasive cancer precursor lesions, which are associated with increased risk for HGSC development, showed a decreased frequency of these lesions in women with a history of oral contraceptive use compared to women without use.[32]

Hormones

The effects of ovulation on ovarian cancer risk are hard to separate from the hormonal involvement, due to the surge of estrogen, progesterone and gonadotropins. A large plethora of epidemiologic studies have implicated steroid hormones in the etiology of ovarian carcinoma. The use of progestin only contraceptives for example is linked to ovarian cancer risk reduction, and pregnancy, where progesterone is the main hormone released, also has risk reducing effects.[33] Additional data on this topic comes from studies on hormone replacement therapy (HRT). Although large numbers of studies have found controversial results on the use of estrogens in HRT, meta analyses on this topic have indicated an ability for estrogens to promote ovarian cancer development.[32]

Inflammation

Another associated risk factor is pelvic inflammatory disease such as endometritis, salpingo-oophoritis and tubo-ovarian abscess formation.[34] Although a number of studies remain inconclusive on the topic, one recent Canadian study identified significant results but only within women who were nulliparous, showed inflammation at an early age or were infertile.[35] More conclusively, recent results of a population-based case control study on the association between aspirin/ NA-NSAIDs and ovarian cancer development, have identified a risk reducing effect for tumor development in the intervention group, suggesting that anti inflammatory drugs may

be protective against ovarian cancer and thus that inflammation may be a risk factor .[36]

2.1.4 Screening and Prevention Strategies

The high mortality of ovarian carcinoma is largely linked to late detection and to the lack of targeted and effective treatment therapies, despite a good initial response to chemotherapy. Current screening strategies in ovarian cancer include the use of CA125, a biomarker used for both diagnosis and monitoring of disease, as well as the use of pelvic ultrasounds.[37]

CA125 however lacks biomarker sensitivity as elevated CA125 levels are only identified in 80% of women with advanced stage and only in 50-60% of women with early stage disease.[37] This biomarker also lacks specificity as it only has positive predictive value in 10% of the cases and can be elevated as a result of other conditions such as pregnancy, endometriosis and colon cancer.[37] Studies like the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial have confirmed that there is no survival benefit of increased screening for ovarian cancer using CA125.[38]

In the search for more effective screening methodologies that will impact on the overall mortality of ovarian cancer, an improved knowledge of tumor biology is necessary. In addition, it is still not clear when in the course of ovarian cancer development the established tumor is curable, if at all. A “window of opportunity” for early detection has been mathematically extrapolated by comparing the prevalence of non-advanced, early stage occult serous cancers identified in prophylactically removed fallopian tubes from women at an increased risk for developing ovarian cancer, with the incidence of HGSC in a comparable population.[39] A period of 4.3 years has been identified when these early stage tumors are histopathologically detectable but clinically asymptomatic and when early detection may save lives.[39]

Unfortunately however, occult early stage tumors are estimated to have a median diameter smaller than 0.9 cm within this early detection period, indicating that a sufficiently sensitive screening test would need to detect tumors less than 0.4 cm in diameter and current screening methods using serum/plasma markers, are only be able to detect tumors in the centimeter diameter range.[39]

The obstacles faced for early detection of these tumors have resulted in a change in focus of many cancer researchers and clinicians, from early detection strategies to the study of preventative measures and identification of risk factors. Currently, the most well accepted preventative measure involves prophylactic BSO surgery in women at an increased genetic risk for ovarian cancer development.[35,40,41] 98% of reduction in risk for ovarian cancer has been observed in the BRCA1/2 mutation carriers who underwent prophylactic (risk reducing) BSO.[1]

2.2 ANATOMY AND HISTOLOGY OF FALLOPIAN TUBE

Fallopian tube is a hollow tubular structure which measures 11-12 cm in length. It runs, in between uterine cornus and ovary, throughout the apex of broad ligament. It has four segments- intramural, isthmus, ampulla, infundibulum and fimbriae.[42]

Mucosa lines the inner aspect of tube and is arranged in branching folds, known as plicae. Microscopically, epithelium is composed of 3 cell types – ciliated, secretory and intercalated (peg). Exceptionally, endocrine cells can be seen. Muscular wall (myosalpinx) is composed of inner circular and outer longitudinal layer.[42]

Lymphatics leave the tubal wall within mesosalpinx, there they join efferent lymphatics from ovary and uterus and terminate in aortic lymph nodes. Other lymphatic channels drain into interiliac and superior gluteal lymph nodes.[42]

2.3 EPITHELIAL OVARIAN CARCINOMA

2. 3. 1 Anatomy and Embryology

During human development the ovaries are formed from the mesoderm layer that gives rise to the coelomic epithelium, which makes up the gonads. In the female, this coelomic epithelium continues to proliferate giving rise to the ovaries and the Mullerian tract.[43,44] As the Mullerian ducts differentiate, they give rise to the fallopian, the endocervical and the uterine epithelium. The ovarian surface epithelium is morphologically similar to as well as continuous with the mesothelial lining of all abdominal and pelvic structures.[44,45] Interestingly, pathologists have identified that tumors diagnosed in the ovarian tissue resemble epithelium from the Mullerian tract rather than the mesothelioma-like ovarian surface epithelium.[46]

These observations have been validated by gene expression studies showing strong similarities between profiles of serous tumors and those of fallopian tube epithelium.[47] Additionally, shared gene expression profiles were also identified between endometrioid carcinomas and normal endometrium, clear cell carcinoma and normal endometrium and mucinous carcinoma and normal colon.[47]

Overall, these data suggested that each of the four ovarian cancer histotypes might originate from different cell types and not from the ovarian surface epithelium. Therefore, the exact origin of the ovarian epithelial tumors has been somewhat unclear and a number of different hypotheses exist to explain this phenomenon.

2.3.2 Origin of Epithelial Ovarian Carcinoma

Despite the identification of ovarian tumors surrounding the ovaries and abdominal regions, HGSC precursor lesions have never been identified in the ovarian tissue. The lack of precursor lesions, despite continued work by pathologists to

understand the tumor progression of ovarian carcinoma, has turned attention towards ovarian cysts.[48,49]

These lesions termed cortical inclusion cysts (CIC) are commonly lined by benign epithelium with occasional dysplastic regions and are located beneath the ovarian surface epithelium in the stroma adjacent to invasive carcinoma. Analysis of these benign lesions, which closely resemble mullerian type tissue, gave rise to the **"second mullerian system"** hypothesis of ovarian cancer development.[46]

Based on this theory, cortical inclusion cysts arise from invaginated mesothelial tissue of the ovarian lining, but undergo metaplastic changes upon exposure to steroid hormones and inflammatory factors, whereby the mesothelium becomes mullerian-like. These mullerian-like lesions, would then give rise to ovarian cancer, replace the ovarian tissue and lead to the formation of adnexal tumors.[46,49]

Limitations of this hypothesis come from the observation that although such mullerian like inclusion cysts are commonly found in the ovary, there have never been any reproducible cancer precursor lesions identified that might explain the transition from such benign lesions to ovarian tumors, particularly on careful study of women at high genetic risk of ovarian cancer undergoing risk-reducing oophorectomies.[46]

2.3.3 Fallopian Tube Hypothesis

In recent years another more compelling hypothesis has emerged and identified the origin of ovarian cancer in the fallopian tube epithelium (FTE) rather than in the ovarian surface epithelium (OSE) (Figure 2).[13]

Additionally, there are also two different hypotheses (a & b) as to how cells from the fallopian tube become transformed and are then identified in the ovarian tissue.

a) **Exfoliation theory**- It presumes that due to the close proximity of the fimbriated end of the fallopian tube to the ovary and its involvement in the pick up of the ovum, exfoliated tubal epithelial cells may be included into the ovarian stroma and form inclusion cysts .[50]

Evidence for this theory comes from the characterization of the ovarian mesothelium, the mullerian tissue from the fallopian tubes and the ovarian tumors. A number of differentiation markers, like BCL2 and PAX8, that are present in epithelial cells from the mullerian ducts, such as the fallopian tubes and which are also present in ovarian tumors, have been identified in the lining of the ovarian inclusion cysts.[50] This observation not only supports the fallopian tube hypothesis, but additionally may also indicate that the tumor transformation of these tube cells occurs in the ovarian stroma.

b) An alternative hypothesis however suggests that the FTE transformation occurs within the fallopian tube, from where tumor cells then migrate to the ovaries during ovulation (Figure 2).[46]

Support for this fallopian tube hypothesis comes from the identification of the ovarian cancer lesions within the FTE and also from characterization studies of these lesions.[51-54]

These lesions were first described in 2001, by Dutch investigators, as **Tubal Intraepithelial Carcinomas (TICs)** and later were designated as **Serous Tubal Intraepithelial Carcinomas (STICs)**.[13]

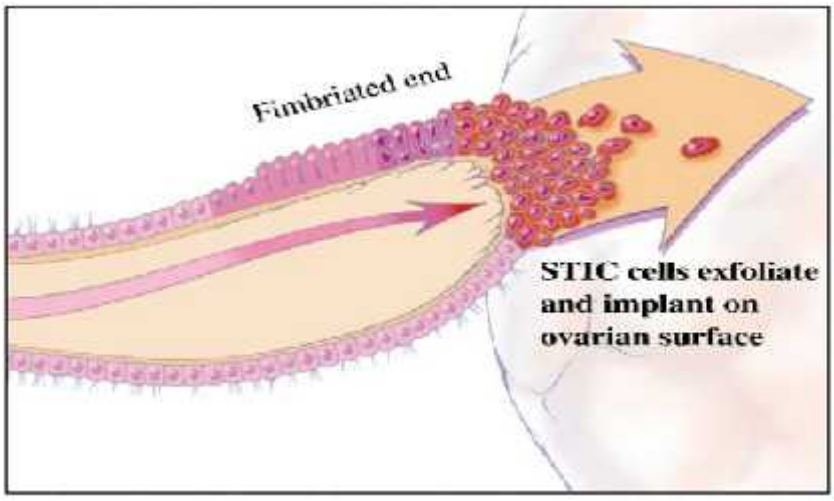

Figure 2: Fallopian tube hypothesis illustrating cellular transformation and metastasis to the ovaries.[13,46]

2.4 FALLOPIAN TUBE AND NONSEROUS OVARIAN CANCER.

Clear Cell Carcinoma (CCC) and Endometrioid Carcinoma (EC) are the next 2 common subtypes of EOC, each accounting for 10% of EOC.[1]

Molecular studies in past decades have shown association of CCC and EC with endometriosis and molecular genetic studies depicted LOH in the same chromosomal regions in endometriosis and EC.[13] Retrograde menstruation accounts for most of the cases of endometriosis, which itself is benign and increases risk of ovarian cancer.[1] Data obtained from Ovarian Cancer Association Consortium (OCAC) suggested that tubal ligation is associated with a 38% and 52% reduction in risk for EC and CCC, respectively, compared to a 19% drop in HGSC.[1] Ligation of fallopian tube would interrupt passage of endometrial tissue to ovary, but the distal epithelial cells would still be able to shed to ovary until fimbriectomy is performed.[1]

Origin of Mucinous tumors and Brenner tumors is puzzling as unlike serous tumors they do not show mullerian phenotype. It has been frequently found that Mucinous tumors and Brenner tumors are associated with Walthard cell nests. These

nests are located at tubal-peritoneal junction and are composed of benign transitional type epithelium.[13]

2.5 PRECURSOR LESIONS AND SEE-FIM PROTOCOL

The Serous Tubal Intraepithelial Carcinoma (STIC) represents the first identifiable pre-malignant lesion in the fimbriated end of the FTE and it has been proposed that earliest neoplastic change begins in secretory cells.[13]

STIC is very uncommon in the general population but is seen more frequently in BRCA mutation carriers undergoing prophylactic bilateral salpingo-oophorectomies, and is seen in as many as 60% of clinically evident HGSC.[51-54]

These lesions contain morphological and molecular alterations that are similar to those identified in HGSC. Mutation analysis of the wild type BRCA allele in STICs from BRCA mutation carriers reveals the presence of somatic mutations, indicating the complete loss of BRCA functionality within these lesions.[53,55] Additional more recent gene expression studies have identified similarities between fallopian tube profiles of BRCA mutation carriers and HGSC profiles, further supporting a close relationship between the STIC and HGSC.[56,57]

The p53 mutation represents the most well established alteration, which is shared between STICs and HGSC.[51,52,58] Additional shared alterations include high proliferation, measured by Ki67, over-expression of P16, FAS, Rsf-1 and CCNE1, Muc-4, stathmin-1 and shortened telomeres.[59,60]

To improve diagnostic reproducibility of STIC, a group of gynecological pathologists developed a diagnostic algorithm incorporating histological and immunohistochemistry features.[61]

Morphological characterization of the STICs include : cellular features such as stratified epithelium, loss of polarity, nuclear enlargement, hyperchromasia,

irregularly distributed chromatin, nucleolar prominence, mitotic activity and absence of ciliated cells.[3,61]

IHC characterization of these lesions includes : p53 and Ki67 stain. p53(+) regions were defined by either diffuse moderate to strong expression of p53 in >75% of the cells or by complete absence of staining, as both these patterns are indicative of p53 mutations.[61]

Ki67 high regions were defined at a threshold of >10% or more positively stained cells, and Ki67 low at a threshold of <10% positive cells, compared to normal FTE which show a proliferative index of only <2% positively stained cells.[61]

- **STIC positivity is determined by any three of the aforementioned morphological abnormalities and by p53(+) and Ki67 high staining.[61]**

The failure in the past to identify the tubal carcinomas was because it was assumed that precursor lesions of ovarian tumors will logically lie in ovaries only and therefore, fallopian tubes were not examined carefully.[46] Moreover, TICs were small, easily to be missed on grossing and were almost always detected in the fimbriae.

Medeiros *et al*[52] have developed a meticulous protocol (SEE-FIM) for carefully evaluating the fallopian tube that maximizes examination of the fimbriae end in order to detect these early carcinomas.

GROSSING PROTOCOL [1,62] –

1. Specimen is fixed in formalin before grossing.
2. Distal 2cm of the fallopian tube is separated from rest of the tube and is then cut longitudinally. Rest of the tube is subjected to cross section at 2-3 mm intervals (Figure 3).

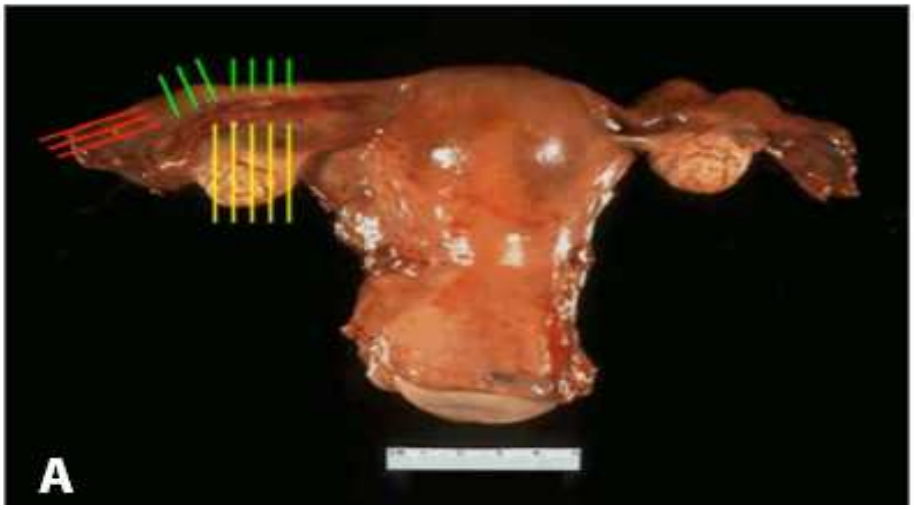

Figure 3: Examination of salpingo-oophorectomy specimen by SEE-FIM protocol.[1]

Careful characterization of the fallopian tube epithelial lesions by the well established SEE-FIM technique has revealed the presence of **Tubal Intraepithelial Lesions (TILs) or Serous Tubal Intraepithelial Lesions (STILs)**, which may be precursors to TICs/ STICs.[54,63]

The term STILs is used to describe a spectrum of epithelial changes ranging from normal appearing epithelium, expressing p53, to the lesions which have increasing degree of atypia but fall short of STIC.[64]

STILs are identified by the presence of any of the same three aforementioned morphological abnormalities along with only p53(+) or Ki67 high regions by IHC analysis.[61]

If the lesions contain fewer than three abnormalities, those regions may be called “suspicious for STICs” and “not suspicious for STICs” if only minor abnormalities are identified.[61]

Additional abnormalities termed “p53 signatures” (or foci), characterized by high p53 immunostaining, are defined as strong nuclear staining obscuring its detail in

at least 12 consecutive secretory nuclei in benign-appearing epithelium of the fallopian tube in both BRCA and non-BRCA mutation carriers.[64]

Kindelberger *et al*[3] performed cross-sectional study on 55 cases containing pelvic serous carcinoma by applying SEE-FIM protocol for all cases. 20/30 cases classified as ovarian carcinoma had TICs; 93% of TICs involved the fimbriae. Out of the 5 ovarian cases with TICs, p53 DNA analysis showed identical mutations in at least one focus of TIC and ovarian cancer.

Medeiros *et al*[52] did case-control study on 13 BPSO and 13 control specimens. On sectioning fimbriae by SEE-FIM protocol, they found 5 cases of early cancers in the fallopian tube. Four out of five stained positive for both p53 and MIB-1.

Powell et al[65] studied 67 BPSO specimens of BRCA mutation carriers and applied the protocol on 41 of them. They found 7 occult malignancies, 4 in fallopian tube and 3 in the ovaries and all 7 were found in specimens in which the protocol was applied.

Callahan *et al*[66] did cross-sectional study on 122 BPSO specimens from women with BRCA1 or BRCA2 mutations by applying SEE-FIM protocol and found 7(5.7%) cases showing occult tubal carcinoma.

Colgan *et al*[67] found 5(8.3%) occult carcinomas (4 located in fallopian tube) in cross-sectional study of 60 prophylactic RRSO specimens that contained 20 fully-sectioned fallopian tubes.

Kauff *et al*[68] studied 98 BRCA mutation carriers who underwent prophylactic RRSO and found 3(3%) cases with occult carcinoma, 2 involving ovaries and 1 in tube.

These results support the origin of serous ovarian cancer in the FTE and also propose the presence of a p53 over-expressing precursor lesion in the development of this disease.

Although the exact proportion of ovarian or peritoneal carcinoma cases which can be attributed to be originating in the distal fallopian tube, remains to be determined by more number of studies, nevertheless, STIC remains a candidate source for these tumors.[3] A follow-up study has shown that the detection frequency of serous tubal intraepithelial carcinomas (STICs) increased from 35% to 50% when random sampling was replaced by the SEE-FIM protocol.[52] The frequent finding of intraepithelial carcinoma in the fallopian tubes suggest that removal of the fallopian tube (salpingectomy) could prevent this type of ovarian cancer, by interrupting the spread of cells to the ovarian or peritoneal surfaces.

So, the SEE-FIM protocol should be employed to estimate involvement of fimbrial end by the precursor lesions and thus could be useful for early detection and prevention of the ovarian tumors.

MATERIAL AND METHODS

Source of data :

The present study included specimens of hysterectomy with bilateral salpingo-oophorectomy received at histopathology section, Department of Pathology, B.L.D.E.U'S Shri B.M. Patil Medical College, Hospital & Research Centre, Vijayapur.

Duration of the study was 1 year & 8 months from 1st November 2013 to 30th June 2015.

Methods of collection of data :

All hysterectomies with bilateral salpingo-oophorectomy having clinical diagnosis of ovarian tumor (study group), received in histopathology section at Department of Pathology were included in the study.

In all these cases detailed examination of fallopian tubes was done by applying SEE-FIM (Sectioning and Extensively Examining the FIMbriated End) protocol. This protocol entailed amputation of each fimbria at the infundibulum, longitudinal sectioning of the fimbria and extensive cross sectioning of the remainder of the tube at 2-3 mm intervals.

Specimens of hysterectomy with bilateral salpingo-oophorectomy, done for other indications apart from ovarian tumor were taken as control group and same protocol was applied on them.

Tissue processing and embedding in paraffin blocks was done and sections of 3-5 micron thickness were prepared which were stained with routine Haematoxylin and Eosin (H&E).

Detailed examination of fallopian tubes was done and classified according to the following group of changes -

- ✓ Tubal intraepithelial carcinoma (TIC) – in this entity entire epithelium is replaced by malignant cells.
- ✓ Tubal intraepithelial lesion (TIL) – includes stratification with nuclear hyperchromasia, overcrowding and mild atypia.
- ✓ Only stratification
- ✓ Negative for any changes

Histological changes in bilateral fallopian tubes were noted and overall change was assigned based on the higher morphological feature. Usefulness of SEE-FIM protocol in identifying fallopian tube precursor lesions was evaluated.

Inclusion criteria:

All hysterectomies with bilateral salpingo-oophorectomy having clinical diagnosis of ovarian tumor.

Exclusion criteria:

1. Non epithelial ovarian tumors like germ cell tumors, sex cord stromal tumors and metastatic tumors.
2. Ovarian tumor coexistent with second primary tumor.

Statistical analysis: Data was analyzed using:

Percentage of various histological changes.

Diagrammatic presentation.

RESULTS

A total of 60 cases were studied over a period of 1 year & 8 months from 1st November 2013 to 30th June 2015. Tubal changes were noted in specimens of hysterectomy with bilateral salpingo-oophorectomy having clinical diagnosis of ovarian tumor (study group) and also in specimens without ovarian tumor (control group) .

AGE

In our study, mean age of women with ovarian tumor was 43 years and median age was 42 years.

Median age of patients with benign tumors was 41 years, for borderline tumors 40 years and for malignant tumors was 48 years. Mean age of women with HGSC was 51 years.

TABLE 1: Distribution of changes in the study group according to Age.

A) AGE GROUP (15-25 YEARS)

Sl. No.	DIAGNOSIS OF OVARY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Benign serous cystadenoma	2	0	1	1	**4**

In the age goup of 15-25 years, we found 4 cases of ovarian tumor. All 4 were diagnosed to be Benign serous cystadenoma. TIC was noted in 2 cases, none of the cases showed changes of TIL, 1 case showed change of stratification and 1 didn't show any changes in the tubes.

B) AGE GROUP (25-35 YEARS)

Sl. No.	DIAGNOSIS OF OVARY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Papillary adenocarcinoma	0	1	0	0	**1**
2	Benign serous cystadenoma	3	1	0	3	**7**
3	Mucinous cystadenoma	1	0	2	0	**3**
4	Benign Brenner tumor	0	0	1	0	**1**
	TOTAL	**4**	**2**	**3**	**3**	**12**

In our study, we got 12 cases in the age group 25-35. One was diagnosed as papillary adenocarcinoma which had tubal changes of TIL. Seven cases were diagnosed as Benign serous cystadenoma , of them 3 showed TIC, 1 TIL and rest were negative for any changes. We got three cases of Mucinous cystadenoma , one of them showed TIC and two had changes of stratification. There was one case of Benign Brenner tumor which showed only stratification.

C) AGE GROUP (35-45 YEARS)

Sl. No.	DIAGNOSIS OF OVARY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Serous cystadenocarcinoma	1	0	0	0	**1**
2	Benign serous cystadenoma	2	1	3	5	**11**
3	Serous cystadenoma (borderline)	0	0	0	1	**1**
4	Mucinous cystadenoma	0	2	0	1	**3**
	TOTAL	**3**	**3**	**3**	**7**	**16**

In our study, we got 16 cases in the age group 35-45. One case was of Serous cystadenocarcinoma which showed changes of TIC in its tube. In total there were 11 cases of Benign serous cystadenoma, of them two had TIC, one had TIL, 3 had change of only stratification and rest were negative for any change. Only one case of Serous cystadenoma (borderline) was there in our study, which showed no changes. Three cases were of Mucinous cystadenoma, 2 of them had TIL and one was negative for any change.

D) AGE GROUP (45-55 YEARS)

Sl. No.	DIAGNOSIS OF OVARY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Serous carcinoma	1	0	0	0	**1**
2	Serous adenocarcinoma	0	1	0	0	**1**
3	Benign serous cystadenoma	3	1	3	2	**9**
4	Benign serous cystadenofibroma	0	0	0	2	**2**
5	Mucinous adenocarcinoma	1	0	0	0	**1**
6	Mucinous cystadenoma	1	0	0	1	**2**
7	Benign Brenner tumor	0	0	1	0	**1**
	TOTAL	**6**	**2**	**4**	**5**	**17**

Majority of the cases were seen in the age group of 45-55 years and the changes of TIC also were more common in this group.

In the present study, we got one case of Serous carcinoma which was positive for TIC, one case of Serous adenocarcinoma which had changes of TIL. There were 9 cases of Benign serous cystadenoma in this age group; 3 with TIC, 1 had TIL, 3 had changes of stratification and 2 were negative for any changes. We got 2 cases of Benign serous cystadenofibroma, both didn't show any changes in their tubes. There was 1 case of Mucinous adenocarcinoma, which was TIC positive. Two cases were of Mucinous cystadenoma, one had TIC and the other one was negative for any change.

We found one case of Benign Brenner tumor which showed changes of stratification in the tubes.

E) AGE GROUP (55-65 YEARS)

Sl. No.	DIAGNOSIS OF OVARY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Serous cystadenocarcinoma	1	0	0	0	**1**
2	Benign serous cystadenoma	0	1	0	0	**1**
3	Papillary cystadenoma	1	0	0	0	**1**
4	Benign serous cystadenofibroma	0	1	0	0	**1**
5	Mucinous cystadenoma	0	0	1	0	**1**
	TOTAL	**2**	**2**	**1**	**0**	**5**

In the present study, there were 5 cases of ovarian tumor in the age group 55-65 years. One case was of Serous cystadenocarcinoma which was positive for TIC. One case of Benign serous cystadenoma, which showed TIL. One case was of Papillary cystadenoma which was TIC positive. Benign serous cystadenofibroma (1 case) showed changes of TIL. We got one case of Mucinous cystadenoma which showed stratification in the tubes.

F) AGE GROUP (65-75 YEARS)

Sl. No.	DIAGNOSIS OF OVARY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Serous adenocarcinoma	1	0	0	0	**1**
2	Serous cystadenocarcinoma	1	0	0	0	**1**
3	Benign serous cystadenoma	0	1	1	0	**2**
4	Papillary cystadenoma	0	0	0	1	**1**
5	Mucinous cystadenoma	0	0	1	0	**1**
	TOTAL	**2**	**1**	**2**	**1**	**6**

In the age group 65-75 years, there were two cases with changes of TIC, one with TIL, 2 had stratification and one was negative for any changes.

TIC was noted in Serous adenocarcinoma and Serous cystadenocarcinoma. TIL was seen in the case of Benign serous cystadenoma. Changes of only stratification were seen in Benign serous cystadenoma and Mucinous cystadenoma. There was one case of Papillary cystadenoma in this group, which was negative for any changes in the tubes.

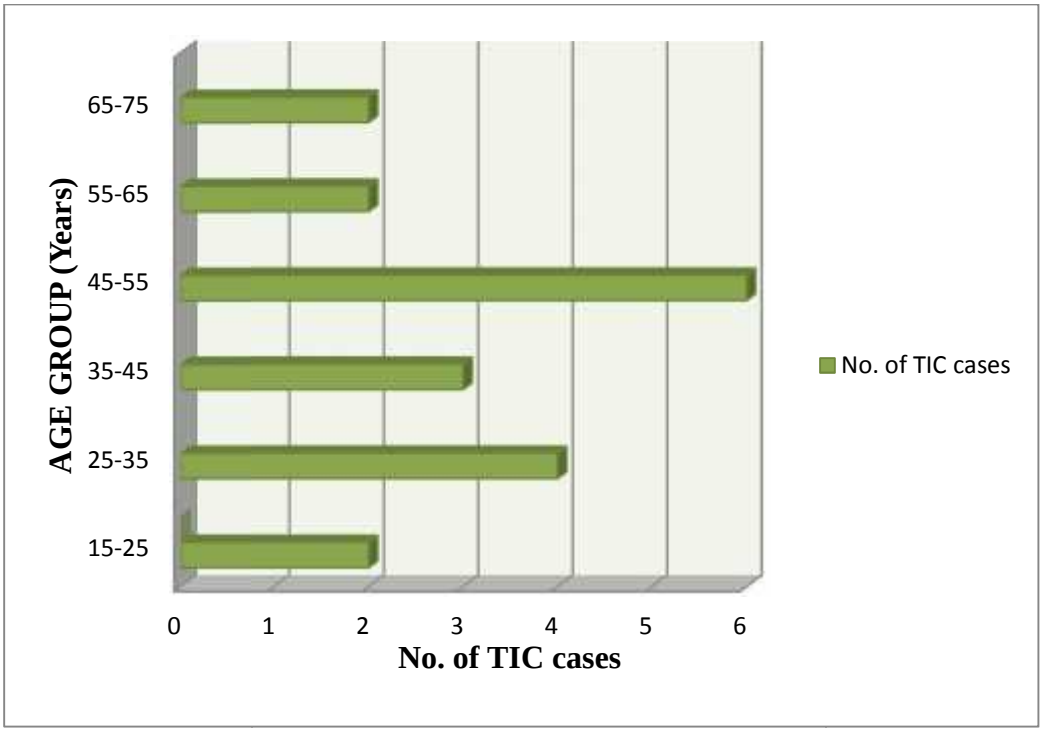

Figure 4: Bar diagram representing number of TIC cases in various age groups.

TABLE 2: Distribution of changes in study group.

Sl. No.	Changes seen	No. of Cases	Percentage %
1	TIC	19	31.67%
2	TIL	10	16.67%
3	Only stratification	14	23.33%
4	Negative for any changes	17	28.33%
	TOTAL	**60**	**100%**

Out of 60 cases of ovarian tumors, 19 (31.67%) cases showed changes of TIC in fallopian tubes, 10(16.67%) cases revealed TIL, 14 cases (23.33%) showed changes of stratification and 17 (28.33%) were negative for any changes in the tubes.

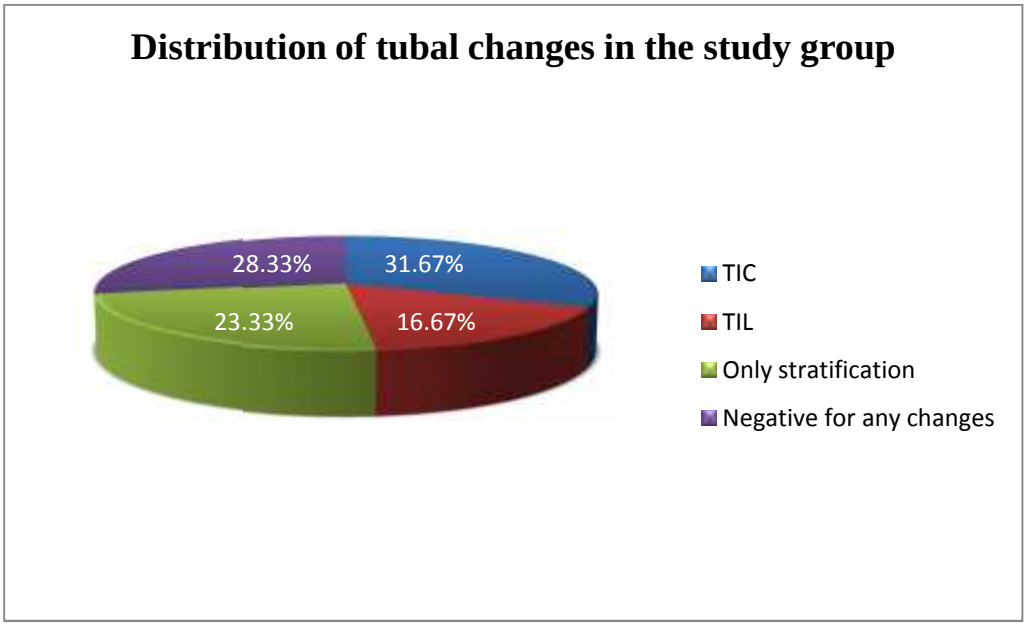

Figure 5: Pie diagram for distribution of tubal changes in the study group.

- Histological changes in fallopian tubes were also studied in specimens without ovarian tumor. Indication for bilateral salpingo-oophorectomy in these specimens were fibroid, DUB, PID, Chronic cervicitis, Bleeding PV, Endometrial hyperplasia/ ?Carcinoma, ?Carcinoma cervix. This was considered as control group.

TABLE 3: Distribution of changes in control group.

Sl. No.	Changes seen	No. of Cases	Percentage %
1	TIC	0	0.00%
2	TIL	4	6.66%
3	Only stratification	16	26.67%
4	Negative for any changes	40	66.67%
	TOTAL	**60**	**100%**

Out of 60 cases, none of the cases showed changes of TIC in fallopian tubes, TIL was noted in 4 (6.66%) cases. 16 cases (26.67%) showed changes of stratification and 40 (66.67%) were negative for any changes in the tubes.

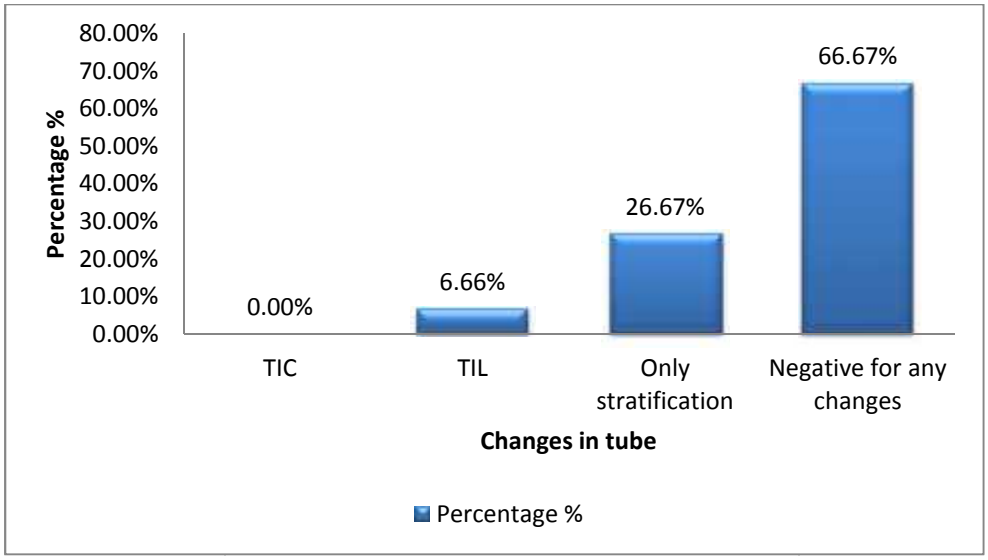

Figure 6: Bar diagram representing distribution of changes in control group.

TABLE 4: Distribution of TIC in ovarian tumors.

TUMORS	No. of cases	TIC positive cases
Benign	51	13
Borderline	1	0
Malignant	8	6
TOTAL	**60**	**19**

In the present study, we got 51 cases of benign tumors, of them 13 had TIC in their tubes. Only one case of borderline tumor was there in our study which was not positive for TIC. Malignant ovarian tumors were 8 in number, out of them 6 were positive for TIC.

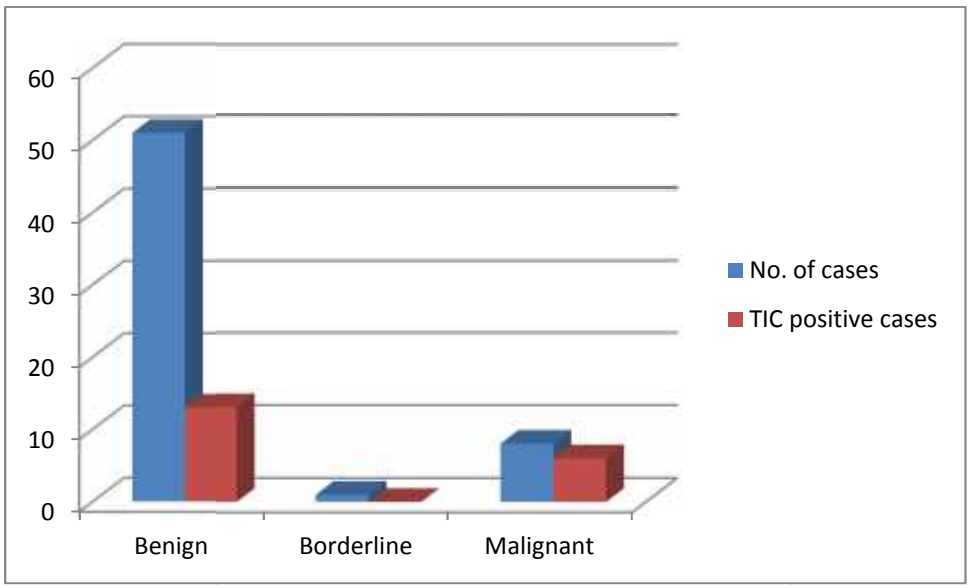

Figure 7: Bar diagram showing distribution of TIC in ovarian tumors.

TABLE 5: Distribution of changes according to ovarian tumors.

Sl. No.	DIAGNOSIS OF OVARY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Serous carcinoma	1	0	0	0	**1**
2	Serous cystadenocarcinoma	3	0	0	0	**3**
3	Serous adenocarcinoma	1	1	0	0	**2**
4	Papillary adenocarcinoma	0	1	0	0	**1**
5	Benign serous cystadenoma	10	5	8	11	**34**
6	Borderline serous cystadenoma	0	0	0	1	**1**
7	Papillary cystadenoma	1	0	0	1	**2**
8	Benign serous cystadenofibroma	0	1	0	2	**3**
9	Mucinous cystadenoma	2	2	4	2	**10**
10	Mucinous adenocarcinoma	1	0	0	0	**1**
11	Benign Brenner tumor	0	0	2	0	**2**
	TOTAL	**19**	**10**	**14**	**17**	**60**

In the present study, 7 cases of HGSC were obtained which included 1 case of Serous carcinoma, 3 cases of Serous cystadenocarcinoma, 2 cases of Serous adenocarcinoma and 1 case of Papillary adenocarcinoma. **Out of the 7 cases, 5 cases (71.43 %) showed changes of TIC in their tubes and rest 2 showed TIL.**

Out of 34 cases of Benign serous cystadenoma, 10(29.41%) cases showed TIC, 5 (14.71%) cases showed changes of TIL. Only stratification was noted in 8 cases (23.53%) and 11 (32.35%) were negative for any changes.

There was one case of Borderline serous cystadenoma which showed no changes in the tubes.

Two cases of papillary cystadenoma were noted, of them 1 (50%) showed TIC changes and the other 1 (50%) case was negative for any changes in the tubes.

Out of 3 cases of Benign serous cystadenofibroma, 1 (33.33%) showed changes of TIL and the rest 2 cases (66.67%) showed no changes at all.

In the present study, there were 10 cases of mucinous cystadenoma. Out of them, 2 (20%) showed TIC, 2 (20%) showed TIL changes, 4 (40%) showed only stratification and rest 2 (20%) were negative for any changes in the tubes.

There was 1 case of Mucinous adenocarcinoma which had changes of TIC in the tubes.

Two cases of Benign Brenner tumor were found, both showed changes of stratification in their tubes.

TABLE 6: Distribution of changes according to indications for BSO in the control group.

Sl. No.	INDICATION FOR BILATERAL SALPINGO-OOPHORECTOMY	TUBAL CHANGES				TOTAL
		TIC	TIL	ONLY STRATIFICATION	NEGATIVE FOR ANY CHANGES	
1	Fibroid, fibroid with PID/DUB	0	3	3	12	**18**
2	PID	0	1	5	14	**20**
3	DUB, DUB with Adenomyosis	0	0	4	8	**12**
4	Chronic cervicitis	0	0	2	2	**4**
5	Bleeding PV	0	0	0	2	**2**
6	Endometrial hyperplasia/? Carcinoma	0	0	2	1	**3**
7	? Carcinoma cervix	0	0	0	1	**1**
	TOTAL	**0**	**4**	**16**	**40**	**60**

Histological changes of TIC were not seen in any of the 60 cases in the control group. In total 4 cases showed TIL, which were noted in cases where bilateral salpingo-oophorectomy was done because of PID and fibroid. Stratification change was noted in 16 cases and rest of the cases (40 cases) had no changes in their fallopian tubes.

TABLE 7: Distribution of HGSC cases.

Ovarian HGSC	No. of cases (%)
Right ovary	3 (43%)
Left ovary	1 (14%)
Bilateral	3 (43%)
Total cases	**7**

In the present study, there were 7 cases of HGSC, of them 3 were involving right ovary, 1 in left ovary and 3 were bilateral.

TABLE 8: Distribution of TIC cases.

Tube involvement	No. of cases (%)
Right tube	10 (53%)
Left tube	4 (21%)
Bilateral tubes	5 (26%)
Total no. of cases	**19**

In our study, we observed changes of TIC in 19 cases. 53% were seen in right tube, 21% in left tube and 26% were seen involving both tubes.

TABLE 9: Distribution of tubal involvement by STIC in HGSC.

Tube involvement in HGSC	No. of cases
Right tube	3
Left tube	1
Bilateral tubes	3
Total no. of HGSC cases	**7**

Out of 7 cases of HGSC, 3 cases had changes of STIC in right tube, 1 case was seen harbouring the change in left tube and 3 cases were noted with bilateral tubal involvement by STIC.

TABLE 10: Distribution of ovarian serous and non serous tumors.

	Mean age	**No. of cases**	**TIC positive cases (%)**
Serous tumors	51	7	5 (71.43%)
Non-serous tumors	48	1	1 (100%)

In the present study, there were 7 cases of serous tumors, with mean age being 51 years. Outf them 71.43% were positive for TIC. There was only one case of non-serous tumor in our study, which was Mucinous adenocarcinoma and was positive for TIC.

PHOTOGRAPHS OF GROSS SPECIMENS

Figure 8: Gross photograph of specimen of uterus with bilateral ovarian tumor.

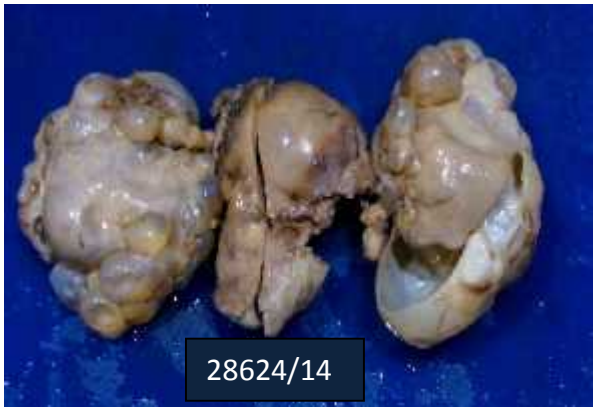

Figure 9: Gross appearance of bilateral serous cystadenoma.

Figure 10: Gross appearance of bilateral serous tumor (1500 ml of serous fluid drained from left ovary and 250 ml from the right ovary).

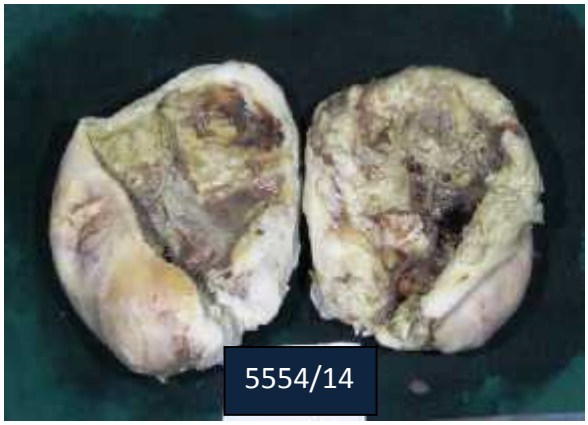

Figure 11: Photograph of bilateral ovarian tumor.

PHOTOMICROGRAPHS

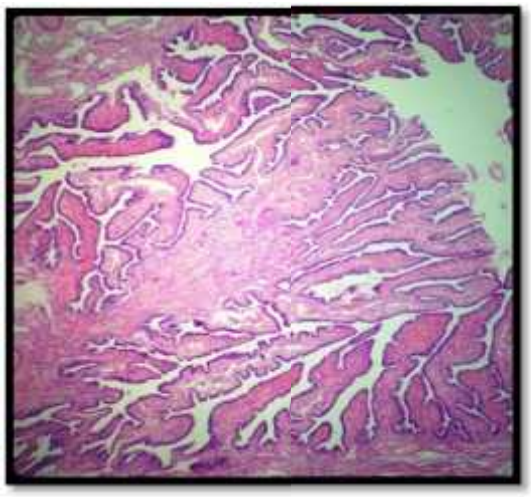

Figure 12: Photomicrograph of fallopian tube, grossed according to SEE-FIM protocol (H&E stain 40x)

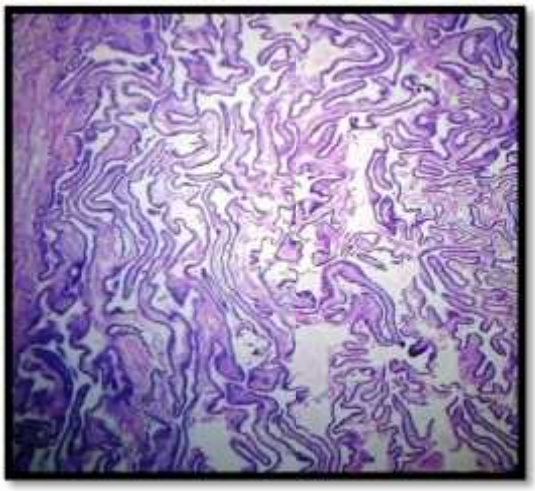

Figure 13: Photomicrograph of fallopian tube, grossed according to SEE-FIM protocol (H&E stain 40x)

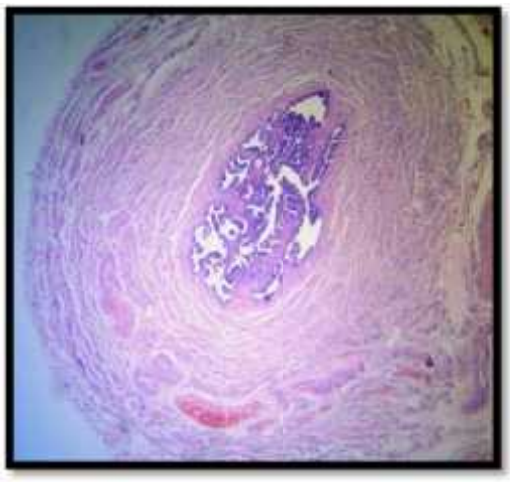

Figure 14: Photomicrograph of fallopian tube, by routine grossing method (H&E stain 40x)

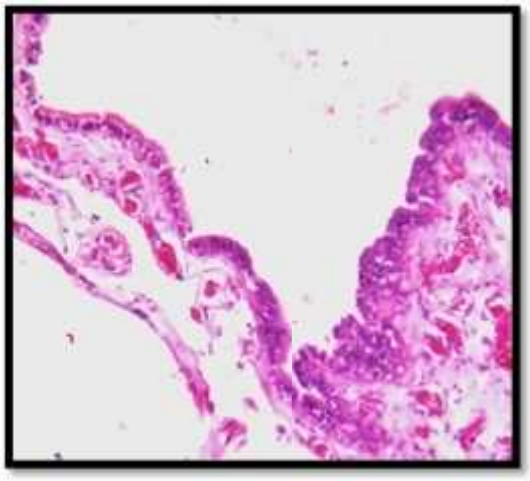

Figure 15: Photomicrograph of TIC, showing nuclear stratification, overcrowding and atypia (H&E stain 100x)

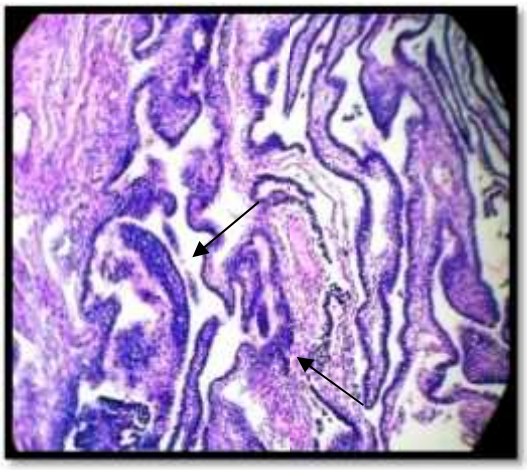

Figure 16: Photomicrograph of TIC (H&E stain 100x)

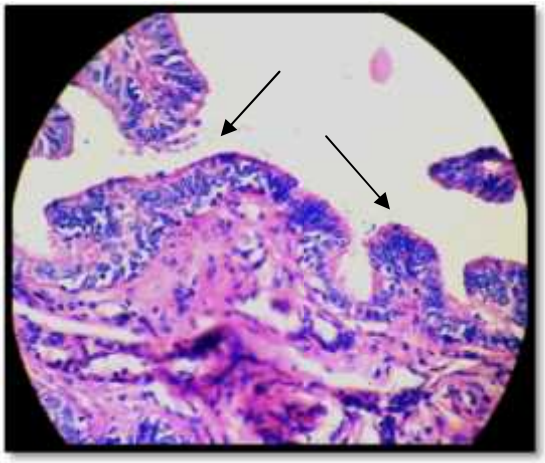

Figure 17: Photomicrograph of TIC, showing nuclear overcrowding, stratification and prominent nucleoli (H&E stain 100x)

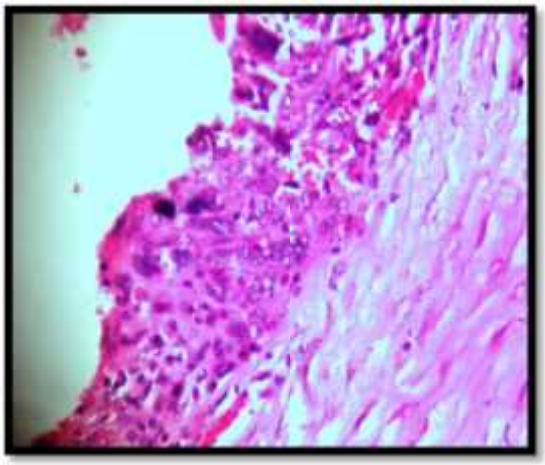

Figure 18: Photomicrograph of TIC, entire epithelium is replaced by malignant cells (H&E stain 400x)

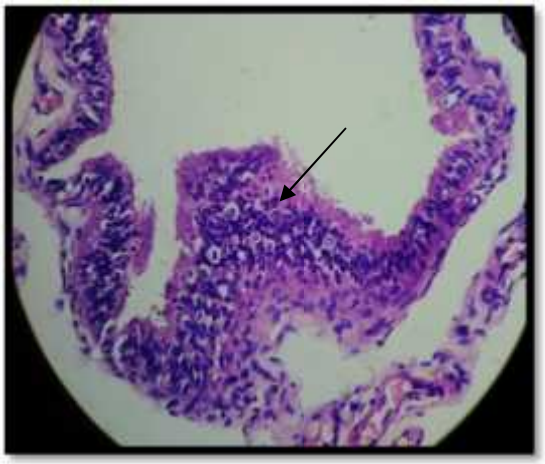

Figure 19: Photomicrograph of TIC, showing nuclear stratification and hyperchromasia with loss of polarity(H&E stain 400x)

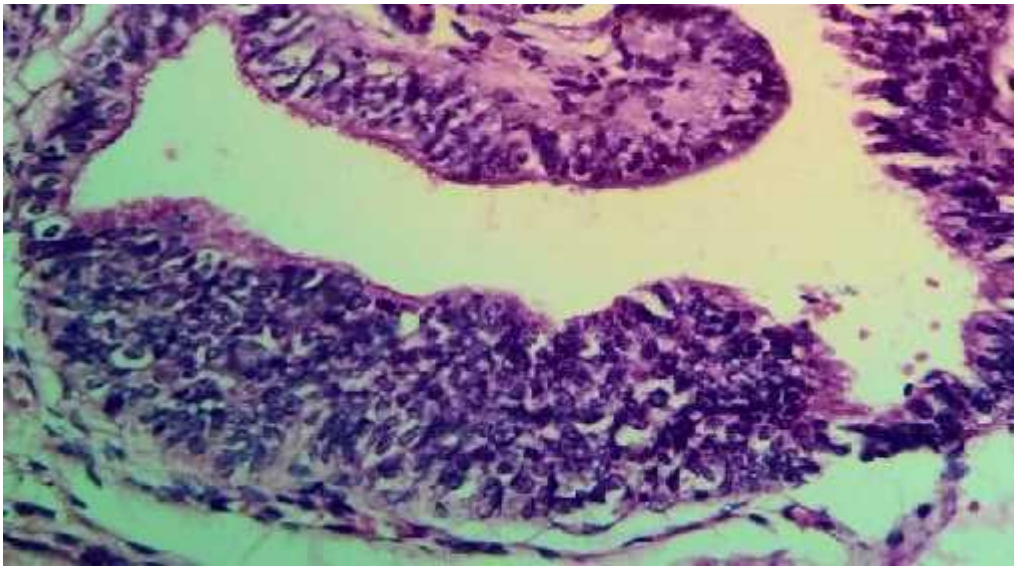

Figure 20: Photomicrograph of TIC, showing loss of polarity,nuclear stratification and prominent nucleoli (H&E stain 400x)

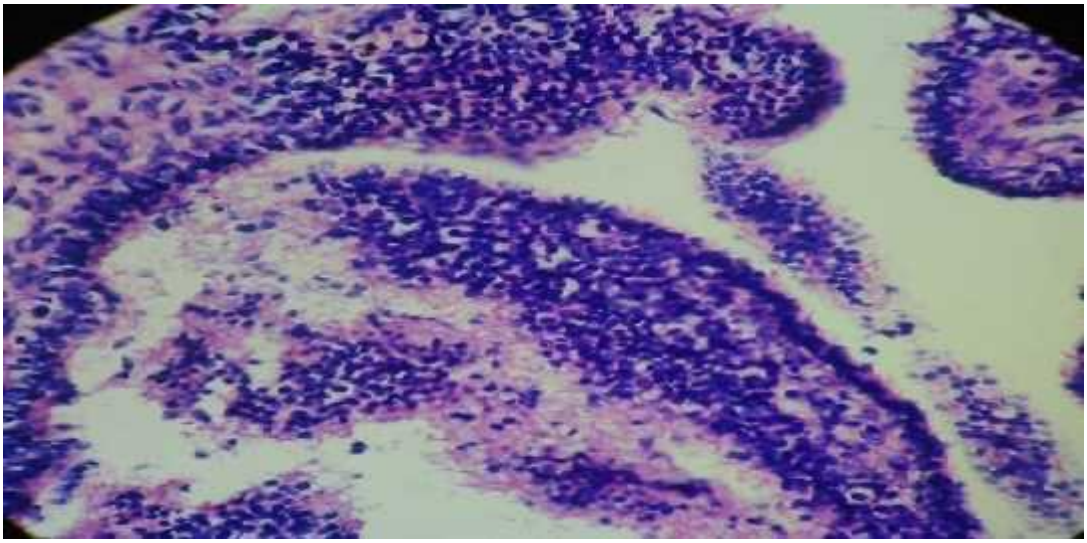

Figure 21: Photomicrograph showing tangential artifact which mimics TIC

(H&E stain 400x)

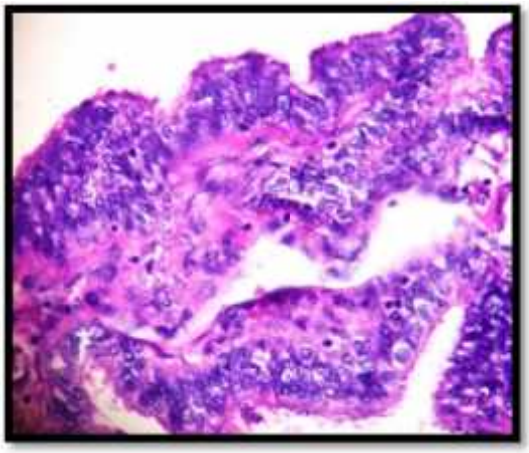

Figure 22: Photomicrograph showing features of TIL (H&E stain 400x)

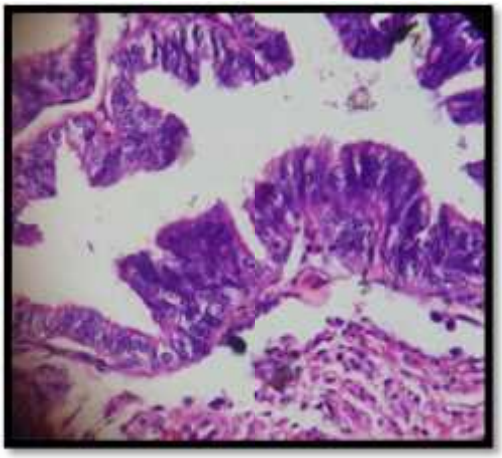

Figure 23: Photomicrograph showing features of TIL (H&E stain 400x)

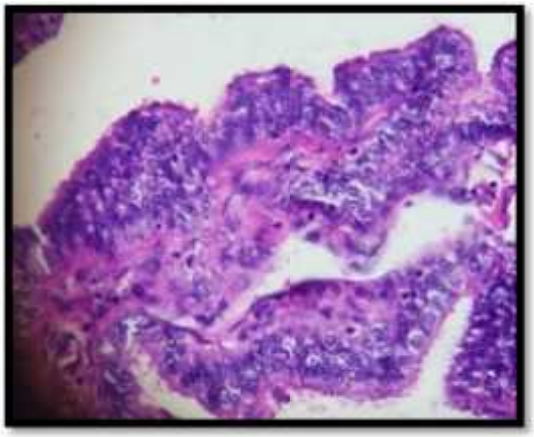

Figure 24: Photomicrograph showing nuclear stratification (H&E stain 400x)

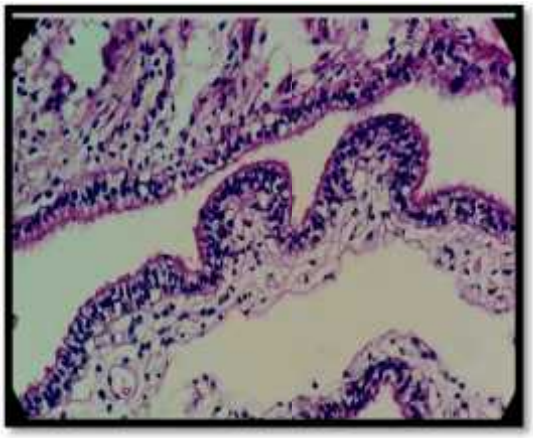

Figure 25: Photomicrograph showing fallopian tube negative for any changes (H&E stain 400x)

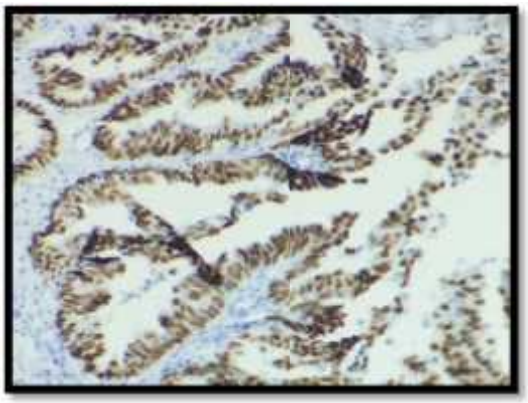

Figure 26: Photomicrograph of fallopian tube showing positivity for p53 (100x)

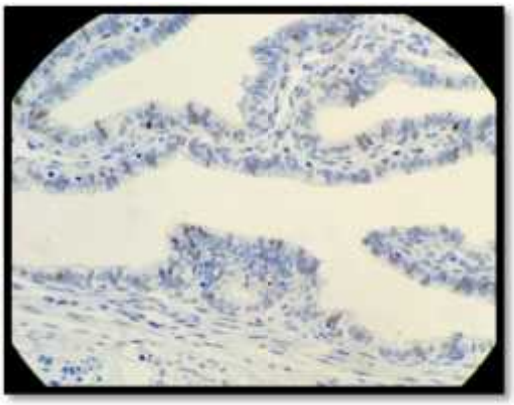

Figure 27: Photomicrograph of fallopian tube showing positivity for p53 (40x)

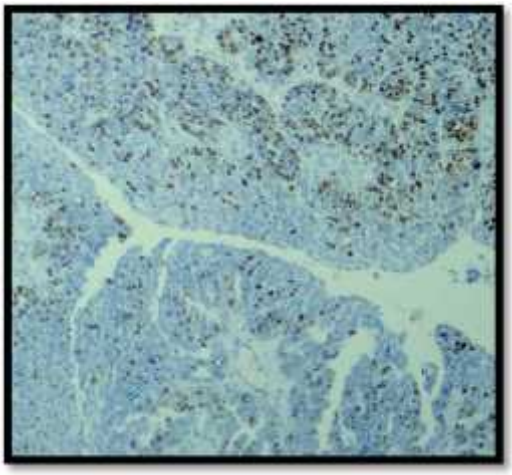

Figure 28: Photomicrograph of fallopian tube showing positivity for MIB-1(Ki67) (100x)

DISCUSSION

Ovarian cancer is the most lethal gynecological cancer and among it, the commonest subgroup is Epithelial Ovarian Carcinomas (EOCs) .

Examination of prophylactic salpingo-oophorectomy specimens in BRCA mutation carriers revealed precursor lesions in the form of early serous malignancies (STICs) in fallopian tube, rather than involving the ovarian surface or within ovarian cortical inclusion cysts.[2]

These unexpected findings in high risk women led to the development of specialized protocol; SEE-FIM protocol, which was found to be helpful in identifying the occult tubal lesions.

STICs are sufficiently small to escape both gross and microscopic examination.[64] They are characterized by TP53 mutations, increased cell proliferation, secretory cell phenotype and similar gene changes as in invasive HGSC.[1] Unlike traditional carcinomas in situ in other sites, they have the capacity to metastasize without invading the salpinx.[64]

In the present study, 60 specimens of hysterectomy with bilateral salpingo-oophorectomy were evaluated for the presence of tubal changes in study and control groups.

In the study group, TIC was observed in 31.67% cases, TIL in 16.67% cases, 23.33% of the cases revealed changes of stratification and 28.33% were negative for any changes in the tubes. Out of 60, 7 cases of HGSC were there and 5 (71.43%) of them showed TIC and rest 2 showed TIL.

In our study population, the mean age was 43 years and median age was 42 years. Maximum number of cases were seen in the age group of 45-55 years.

Table 11: Comparison of Median age at cancer.

Studies	Powell *et al*[65]	Present study
Age (median)	53	42

In our study, the median age of women with cancer was 42 years and in the study by Powell *et al* [65] it was 53 years.

Table 12: Comparison of Median age for Benign and Malignant tumors.

Studies	**Age (median)**	
	Benign cases	**Malignant cases**
Callahan *et al*[66]	46	61
Present study	41	48

The median age of women with benign tumors was 41 years in our study which is comparable to the study by Callahan *et al*[66] (46 years).

Median age for malignant tumors was observed as 48 years in our study and as 61 years in the study by Callahan *et al.*[66]

Table 13: Comparison of Tubal malignancy in Age ñ 44 years.

Studies	**TIC positive**		**Total no. of TIC cases**
	Age ñ 44 years.	**Age < 44 years**	
Callahan *et al*[66]	7 (100%)	0 (0%)	7
Present study	11 (58%)	8 (42%)	19

Callahan *et al*[66] got all TIC positive cases (100%) in the age ñ 44 years whereas, in our study, 58% of cases bearing changes of TIC were seen in the age ñ 44 years and 42% cases of TIC positive were seen in less than 44 years of age.

These observations of tubal malignancy being more common in age ñ 44 years is substantiating the fact that increasing age has more likelihood of occult tubal malignancy.

Table 14: Comparison of Percentage (%) of STIC with other studies.

Studies	Study population	No. of cases of ovarian serous carcinoma	No. of cases of STIC	Percentage (%) of STIC
Kindelberger *et al* [3]	55	30	20	66.67 %
Przybycin *et al*[69]	37	33	20	60.61 %
Present study	60	7	5	71.43 %

In the present study, STIC was observed in 71.43 % cases of HGSC which is comparable to the other studies. Kindelberger *et al*[3] found STIC in 66.67 % and Przybycin *et al*[69] in 60.61 % cases.

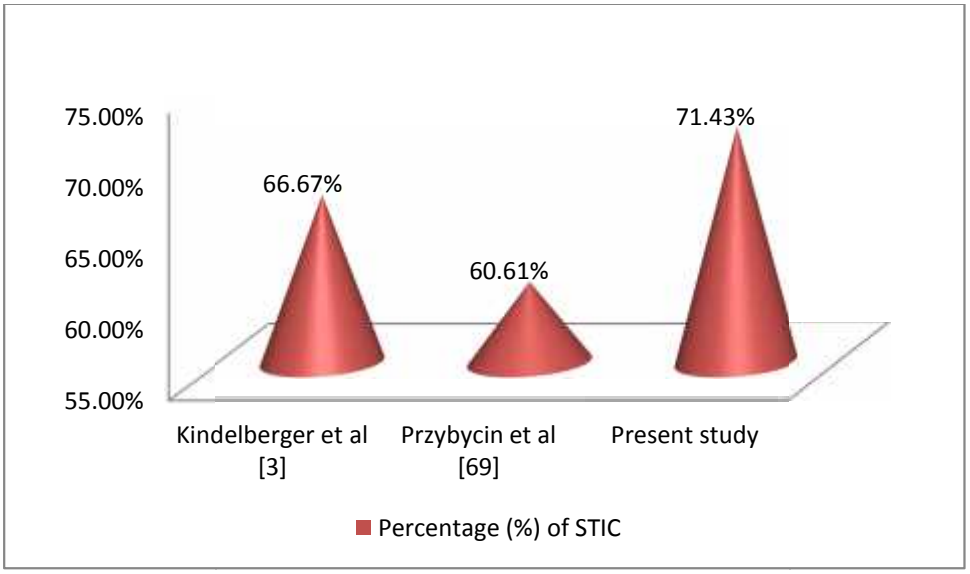

Figure 29: Bar diagram showing comparison of STIC with other studies.

Table 15: Comparison of distribution of HGSC cases.

Ovarian HGSC	Gao *et al*[70]	Present study
Right ovary	6 (20%)	3 (43%)
Left ovary	4 (13%)	1 (14%)
Bilateral	20 (67%)	3 (43%)
Total cases	**30**	**7**

Majority of the cases of HGSC were found to be bilateral in our study (43%). Similar finding was seen in the study by Gao *et al*[70] which showed 67% bilateral involvement.

Table 16: Comparison of Distribution of TIC cases.

Tube involvement	Gao *et al*[70]	Present study
Right tube	16 (53%)	10 (53%)
Left tube	8 (27%)	4 (21%)
Bilateral tubes	6 (20%)	5 (26%)
Total no. of cases	**30**	**19**

Majority of the TIC cases were seen to be involving the right tube. In our study 53% of the STIC cases were found in the right tube which is similar to the finding by Gao *et al.*[70] Left tube was harbouring TIC in 21% of the cases in our study as compared to 27% in the study by Gao *et al*[70] We noted bilateral tubal involvement in 26% whereas Gao *et al*[70] noted it in 20% of the cases.

Table 17: Comparison of U/L tubal involvement by STIC in HGSC.

Studies	No. of cases of HGSC	No. of cases with U/L STIC	Percentage (%)
Gao *et al*[70]	30	24	80%
Present study	7	4	57 %

In the present study, STIC was found to be involving unilateral tubes in 57% of the cases of HGSC whereas the study by Gao *et al*[70] showed 80% of cases with unilateral involvement. The higher percentage in Gao *et al*[70] can be attributed to more number of HGSC cases.

Table 18: Comparison of ovarian serous carcinoma.

Studies	Mean age (years)	No. of cases	No. of STIC cases
Tang *et al*[71]	66	32	6 (18.75%)
Present study	51	7	5 (71.43%)

The mean age for ovarian serous tumors in our study was 51 years as compared to 66 years in the study by Tang *et al.*[71] In the present study, STIC was observed in 71.43% of HGSC cases as compared to low percentage of 18.75 in the study by Tang *et al.*[71]

Table 19: Comparison of ovarian non serous carcinomas.

Studies	Mean age (years)	No. of cases	No. of TIC cases
Tang *et al* [71]	56	14	0
Present study	48	1	1

Tang *et al*[71] had examined 14 nonserous ovarian malignancies for the frequency of tubal intraepithelial carcinoma, but none of them showed changes of TIC.

In the present study we found one case of bilateral mucinous adenocarcinoma in woman aged 48 years, which showed changes of TIC in the tubes.

We didn't find any cases of Clear cell carcinoma, Endometrioid carcinoma, Malignant Brenner tumor in our study.

Table 20: Comparison of borderline serous tumor cases.

No. of cases	Tang *et al*[71]	Present study
Borderline serous tumor	10	1
STIC	0	0

There were no changes of STIC in borderline serous tumor cases as observed in our study and also in the study by Tang *et al.*[71]

Table 21: Comparison of mucinous carcinoma cases.

No. of cases	Przybycin *et al*[69]	Present study
Mucinous carcinoma	1	1
TIC	0	1

In the present study we found one case of mucinous carcinoma, which showed changes of TIC in the tubes. Przybycin *et al*[69] also got one case of mucinous carcinoma but the tubes didn't harbour TIC.

Table 22: Comparison of the control group (group with no ovarian malignancy).

Studies	No. of cases	TIC positive
Medeiros *et al*[52]	13	0
Piek *et al*[53]	13	0
Present study	60	0

In the present study, 60 cases of hysterectomy with bilateral salpingo-oophorectomy, done for other indications apart from ovarian tumor were taken as control group and same protocol was applied on them. But none of the cases showed changes of TIC. This is comparable with the study by Medeiros *et al*[52] and Piek *et al.* [53]

Although 4 cases in the control group were harbouring changes of TIL and 16 cases with stratification.

This can be attributed to factors like inflammation, menstruation, ovulation, OCP use, breastfeeding and parity. All these factors have an impact on the microenvironment of fallopian tube leading to the above mentioned histological changes.[1]

Benign tumors

In the present study, we found 51 cases of benign ovarian tumors which included; 34 cases of benign serous cystadenoma, 3 cases of benign serous cystadenofibroma, 2 cases of papillary cystadenoma, 10 cases of mucinous cystadenoma and 2 cases of benign brenner tumor.

In all these cases, TIC and TIL were observed in various percentages. Changes of TIC were observed in 25% cases. This percentage is quiet lower than that seen in overall all malignant cases (7 HGSC and 1 mucinous adenocarcinoma), which showed 75% cases with TIC.

In the study by Tang *et al*,[71] there was no STIC identified among 90 cases of benign conditions.

- These observations in benign tumors, non serous tumors and those of the control group, substantiates the fact that the **frequency of TIC is lower in nonserous gynecologic malignancies and in benign gynecologic neoplasms as compared to ovarian serous carcinomas.**

FUTURE DIRECTIONS

TIC merits close attention as a candidate source for ovarian tumors and must be incorporated into future discussions of the classification of tumors currently designated as primary peritoneal and ovarian serous carcinomas. The genetic changes accompanying and preceding these lesions may then be able to be targeted in prevention studies. In addition, classification of TIL would help in internal validity of studies. Further prospective data is needed to assess interactions between exposures and these lesions.

The SEE-FIM protocol should be employed to provide a precise estimate of fimbrial involvement. Similar efforts should eventually clarify the role of the fimbria in pelvic serous carcinogenesis, tumor classification and possibly, serous cancer prevention.

CONCLUSION

- ✓ Despite the identification of ovarian tumors in the ovaries proper, pelvic and abdominal regions, the precursor lesions have never been identified in the ovarian tissue. Infact examination of salpingo-oophorectomy specimens in high risk women revealed precursor lesions in the fimbrial end of fallopian tube, namely, serous tubal intra-epithelial carcinoma (STIC). So, it can be said that **"ovary is just the soil in which seeds from elsewhere are planted"**.
- ✓ On this discovery, SEE-FIM protocol was designed. It entailed on increasing the surface area of the fimbria available for examination by 60% and thus increase the possibility of detecting the precursor lesions.
- ✓ In the present study we evaluated this protocol to identify the precursor lesions and we observed that 31.67% of the ovarian tumors harboured TIC and 71.43% of the HGSC had STIC.
- ✓ The data implicating fimbrial end of fallopian tube as the primary site of high-grade serous carcinoma will have an important implication in the future, for the development of new approaches for early detection, treatment and prevention of this highly lethal disease.

PITFALLS / LIMITATIONS

- Possibility of misdiagnosing benign epithelial changes and tangential sectioning artifact as carcinoma.
- The exact proportion of ovarian serous carcinoma cases that can be attributed to be originating in the distal fallopian tube remains to be determined by larger studies.
- The current study is limited to morphologic identification only.
- Additional molecular genetic studies are necessary to establish that STIC is the earliest form of carcinoma rather than intraepithelial spread from adjacent invasive serous carcinoma of ovarian or peritoneal origin.

SUMMARY

Ovarian cancer is the leading cause of death due to gynecologic malignancies, accounting for 3% of all cancer diagnosis. HGSC is the most common and lethal subtype. Although deciphering the pathogenesis of ovarian cancer has been challenging, many studies have suggested the correlation between fimbrial end of fallopian tube and ovarian tumors by substantiating the fact that precursor lesion lies in the fallopian tube rather than the ovary. The lesions were named as tubal intra-epithelial carcinomas (TICs) and tubal intra-epithelial lesions (TILs). On the basis on this hypothesis, SEE-FIM protocol was designed and it has been shown that the detection frequency of TICs increased from 35% to 50% when random sampling was replaced by the SEE-FIM protocol.

In the present study, we applied SEE-FIM protocol on 60 specimens of hysterectomy with bilateral salpingo-oophorectomy and observed that 71.43% of the HGSCs and 31.67% of the ovarian tumors had histological changes of TIC.

The frequent finding of intraepithelial carcinoma in the fallopian tubes of women with ovarian tumor, especially in HGSC, suggests that removal of the fallopian tube (salpingectomy) could prevent this type of ovarian cancer, by interrupting the spread of cells to the ovarian or peritoneal surfaces.

The direct evidence regarding STIC as the precursor of HGSC is still tantalizing. Further molecular genetic studies are required to address this important question.

We hope this new perspective of fallopian tube STIC-ing to ovarian cancer, evaluated with the help of SEE-FIM protocol, will be useful for future research on ovarian tumors.

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ANNEXURE-I

ETHICAL CLEARANCE

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

OUTWARD No. 557/2015 Date 10/10/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 10/10/2015 at 03-30 pm scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title "Evaluation of See-Fim (Sectioning & extensively Examining the fimbriated end) protocol in identifying fallopian tube precursor lesions in women with ovarian tumours"

Name of P.G. Student : Dr Swati Patil
Dept of Pathology

Name of Guide/Co-investigator : Dr D.R Yelikar
Prof & HOD. Dept of Pathology

DR.TEJASWINI VALLABHA
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586101

Following documents were placed before E.C. for Scrutinization
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

ANNEXURE-II

SAMPLE INFORMED CONSENT FORM

TITLE OF THE PROJECT : Evaluation of SEE-FIM (Sectioning and Extensively Examining the FIMbriated end) protocol in identifying fallopian tube precursor lesions in women with ovarian tumors.

PRINCIPAL INVESTIGATOR : Dr. Swati Arora
P.G.
Department of Pathology

P.G.GUIDE : Dr. B.R. Yelikar
Professor and Head,
Department of Pathology

PURPOSE OF RESEARCH:

Identification of precursor lesions in the fallopian tubes in patients with ovarian tumors by SEE-FIM protocol which could be useful for early detection and prevention of these carcinomas.

PROCEDURE:

All the patients recruited for study will be clearly explained about the reason for study and for selecting them as subjects for the study. They will be explained about risks, benefits and confidentiality of the study. They are allowed to make a free choice of their own for inclusion in the study. They are also informed that there will not be any kind of financial burden on the patients. They are also told about the necessity for follow-up and furnishing of additional information when required.

RISK AND DISCOMFORTS: Not Applicable.

BENEFITS:

I understand that my participation in the study will have no direct benefit to me other than the potential benefit of the treatment.

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record and will be subjected to confidentiality and privacy regulations of the hospital. If the data is used for publications the identity of patient will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw from the study at any time.

I have read and fully understood this consent form. Therefore I agree to participate in the present study.

_____ _____

Participant / Guardian Date:

_____ _____

Signature of Witness Date:

I have explained the patient the purpose of the study, the procedure required and possible risk and benefit to the best of my ability in the vernacular language.

_____ _____

Investigator / P.G. Date:

_____ _____

Witness to Signature Date

ANNEXURE-III

SCHEME OF CASE TAKING

Case No: Date :

Particulars of the patient :

Name :

Age :

O.P.D/I.P.D No. :

Address :

Occupation:

Religion :

Presenting complaints and duration :

Menstrual history:

Obstetric history:

Past history:

Family history:

Personal history:

General physical examination:

Systemic examination:

Radiological Investigations:

Clinical diagnosis:

Examination of Specimen:

- Macroscopic Examination

- Microscopic Examination

- Diagnosis

- Microscopic Findings in Fallopian tube(Fimbrial end)

  TIC

  TIL

  Only stratification

  Negative for any changes

- Final interpretation

KEY TO MASTER CHART

Ov – Ovarian

U/R – Unremarkable

TIL – Tubal Intraepithelial Lesion

TIC – Tubal Intraepithelial Carcinoma

Str - Stratification

BSO - Bilateral salpingo-oophorectomy

PID –Pelvic inflammatory disease

DUB – Dysfunctional uterine bleeding

PV – Per vagina

MASTER CHART

STUDY GROUP

Sl. No.	Name	Age	OPD/IPD No.	HPR No.	Clinical diagnosis	HPR Diagnosis of Right ovary	Changes in Right tube	HPR Diagnosis of Left ovary	Changes in Left tube	Overall change in tube
1	Shantabai	50	2095/13	5514/13	Ov tumor	Benign serous cystadenoma	Only Str	Benign serous cystadenoma	Only Str	Only Str
2	Sufiya	38	2570/13	6040/13	Ov cyst	U/R	Negative	Benign serous cystadenoma	Negative	Negative
3	Mahadevi	35	1408/13	6089/13	Ov cyst	Benign serous cystadenoma	TIL	U/R	Negative	TIL
4	Salima	28	321/14	85/14	Ov cyst	Benign serous cystadenoma	TIC	Cystic follicle	Negative	TIC
5	Kantawwa	45	D/48/14	754/14	Ov cyst	Serous adenocarcinoma	TIL	U/R	Negative	TIL
6	Bibihajaran	42	4596/14	1041/14	Ov cyst with partial torsion	Mucinous cystadenoma	Negative	U/R	Negative	Negative
7	Shantabai	55	5372/14	1438/14	Ov cyst	U/R	Negative	Mucinous cystadenoma	Only Str	Only Str
8	Shaila	55	D/118/14	1826/14	Ov cyst	Serous cystadenocarcinoma	TIC	U/R	Negative	TIC
9	Laxmi	48	9685/14	2549/14	Ov cyst	Benign serous cystadenoma	TIC	Benign serous cystadenoma	TIL	TIC
10	Khatumbi	45	11727/14	2595/14	Ov cyst	U/R	Negative	Benign Brenner tumor	Only Str	Only Str
11	Geeta	32	D/158/14	2614/14	Ov cyst	Mucinous cystadenoma	Only Str	U/R	Negative	Only Str
12	Ashwini	48	13374/14	2886/14	Ov tumor	Serous carcinoma	TIC	U/R	Negative	TIC
13	Lalabai	40	27302/14	2904/14	Ov cyst	Mucinous cystadenoma	TIL	U/R	Negative	TIL
14	Rukmabai	29	27466/14	2978/14	Ov mass	Benign serous cystadenoma	Negative	U/R	Negative	Negative
15	Kasturi	35	27497/14	3012/14	Ov cyst	Benign serous cystadenoma	Negative	U/R	Negative	Negative
16	Sunanda	42	27537/14	3146/14	Ov cyst	Benign serous cystadenoma	Only Str	U/R	Negative	Only Str
17	Zulekha	48	27564/14	3252/14	Cystic ovaries	Benign serous cystadenofibroma	Negative	Benign serous cystadenofibroma	Negative	Negative
18	Indira	47	27566/14	3269/14	Ov cyst	Benign serous cystadenoma	Negative	U/R	Negative	Negative
19	Shantabai	68	27576/14	3384/14	Ov cyst	Benign serous cystadenoma	TIL	U/R	Negative	TIL
20	Riyana	30	27589/14	3421/14	Ov cyst	Benign serous cystadenoma	TIL	U/R	Negative	TIL
21	Parveen	40	27651/14	3623/14	Tubo-Ov mass ? Tumor	Benign serous cystadenoma	Negative	U/R	Negative	Negative
22	Sanjeevani	45	914/14	3775/14	Ov cyst	U/R	Negative	Benign serous cystadenofibroma	Negative	Negative
23	Bhagirati	45	1123/14	3795/14	Ov cyst	U/R	Negative	Benign serous cystadenoma	TIL	TIL
24	Lakabee	70	212786/14	3799/14	Ov cyst	U/R	Negative	Papillary cystadenoma	Negative	Negative
25	Gangabai	65	D/197/14	4047/14	Ov cyst	Serous cystadenoma	Negative	Serous cystadenocarcinoma	TIC	TIC
26	Shaila	25	22211/14	4400/14	Ov cyst	Benign serous cystadenoma	TIC	U/R	Negative	TIC
27	Indrabai	50	299412/14	4853/14	Ov cyst	U/R	Negative	Benign serous cystadenoma	Only Str	Only Str
28	Hameeda	28	D/202/14	4857/14	Ov cyst	U/R	Negative	Benign serous cystadenoma	Negative	Negative
29	Kashiba	40	26960/14	4994/14	Ov cyst	Cystic follicle	Negative	Benign serous cystadenoma	Negative	Negative
30	Shreedevi	40	306782/14	5017/14	Ov mass	Benign serous cystadenoma	Negative	Cystic follicle	Negative	Negative

31	Parvati	58	1658/14	5137/14	Ov mass	Benign serous cystadenoma	TIL	U/R	Negative	TIL
32	Savita	30	1664/14	5169/14	Twisted Ov mass	Mucinous cystadenoma	Only Str	U/R	Negative	Only Str
33	Suman	42	18564/14	5201/14	Ov cyst	Mucinous cystadenoma	TIL	U/R	Negative	TIL
34	Laxmibai H	45	28720/14	5323/14	Ov cyst	Benign serous cystadenoma	TIC	U/R	Negative	TIC
35	Laxmibai M	58	28552/14	5445/14	Ov mass	U/R	Negative	Benign serous cystadenofibroma	TIL	TIL
36	Kavya S	20	28554/14	5464/14	Ov cystic mass	U/R	Negative	Benign serous cystadenoma	TIC	TIC
37	Laxmi G	21	28587/14	5578/14	Ov mass	Benign serous cystadenoma	Negative	U/R	Negative	Negative
38	Mahadevi	40	28664/14	5643/14	Ov cyst	Benign serous cystadenoma	Only Str	U/R	Negative	Only Str
39	Savitha	41	1036/14	5732/14	Ov cyst	Benign serous cystadenoma	TIC	U/R	Negative	TIC
40	Shrekha	34	1789/14	5734/14	Ov cyst	U/R	Negative	Benign Brenner tumor	Only Str	Only Str
41	Leela	45	1844/14	5794/14	Ov cyst	Mucinous cystadenoma	Negative	U/R	Negative	Negative
42	Satawwa	50	1863/14	5796/14	Ov cyst	U/R	Negative	Benign serous cystadenoma	TIC	TIC
43	Nasamma	21	1890/14	5914/14	Ov cyst	Benign serous cystadenoma	TIC	U/R	Negative	TIC
44	Husenbanu	32	28624/14	6036/14	Ov cystic mass	Benign serous cystadenoma	TIC	Benign serous cystadenoma	TIC	TIC
45	Sushilabai	65	28642/14	6221/14	Ov cyst	Mucinous cystadenoma	Only Str	U/R	Negative	Only Str
46	Nandini	28	28660/14	6245/14	Ov cystic mass	Mucinous cystadenoma	TIC	U/R	Negative	TIC
47	Lalita V.Patil	33	28941/14	6314/14	Ov cyst	Benign serous cystadenoma	Negative	U/R	Negative	Negative
48	Parwatewwa	70	28938/14	6452/14	Ov cyst	Benign serous cystadenoma	Only Str	U/R	Negative	Only Str
49	Nagamma	35	28916/14	6549/14	Ov cystic mass	U/R	Negative	Benign serous cystadenoma	TIC	TIC
50	Shavamma	55	S/153/14	6612/14	Ov cyst	Papillary cystadenoma	TIC	Follicular cyst	TIC	TIC
51	Jyoti Kamble	18	416463/14	6687/14	Ov cyst	Benign serous cystadenoma	Only Str	U/R	Negative	Only Str
52	Sangeeta	45	D/2180/15	413/15	Ov cyst	Mucinous cystadenoma	TIC	U/R	Negative	TIC
53	Kamurthin	44	2219/15	416/15	Ov cyst	Serous cystadenocarcinoma	TIC	Serous cystadenocarcinoma	TIC	TIC
54	Sulochana	48	76655/15	1300/15	Ov cyst	Mucinous adenocarcinoma	TIC	Mucinous adenocarcinoma	TIC	TIC
55	Sushila	69	98114/15	1585/15	Ovarian tumor	Serous adenocarcinoma	TIC	Serous adenocarcinoma	TIC	TIC
56	Gouravva	40	30225/15	3042/15	Torsion ovary, ? Mass	U/R	Negative	Serous cystadenoma (borderline)	Negative	Negative
57	Kasturibai	50	D/232/15	3714/15	Ov cyst	Benign serous cystadenoma	Negative	U/R	Negative	Negative
58	Seeta	38	8664/15	3762/15	Ov cyst	Benign serous cystadenoma	Only Str	U/R	Only Str	Only Str
59	Gauramma	50	17395/15	3764/15	Ov cyst	Simple cyst of ovary	Negative	Benign serous cystadenoma	Only Str	Only Str
60	Pramila	30	22379/15	4763/15	Ov mass	Papillary serous adenocarcinoma	TIL	Papillary adenocarcinoma	TIL	TIL

CONTROL GROUP

Sl. No.	NAME	AGE	IPD/OPD No.	HPR No.	INDICATION FOR BSO	TUBAL CHANGES
1	Sudha	61	1567/13	5453/13	Fibroid	Negative
2	Chennamma	38	2738/13	6061/13	Chronic cervicitis	Negative
3	Shankarewwa	60	33306/13	6235/13	PID	Only Str
4	Shashikala	40	33832/13	6253/13	Fibroid	TIL
5	Prabhavati	45	P27391/14	102/14	PID	Negative
6	Kamalabai	45	P27411/14	357/14	Fibroid	Negative
7	Gourawwa	33	D/51/14	404/14	Chronic cervicitis	Only Str
8	Gangamma	45	D/158/14	565/14	DUB	Negative
9	Shakera	35	P27444/14	732/14	PID	Negative
10	Roopa	28	P27476/14	756/14	PID	Negative
11	Gundamma	40	26199/14	804/14	DUB	Negative
12	Bauramma	40	P23107/14	910/14	Chronic cervicitis	Only Str
13	Nirmala	48	2950/14	960/14	Fibroid with DUB	Negative
14	Parvati	44	D/161/14	986/14	DUB	Only Str
15	Kasturibai	45	P27477/14	1032/14	PID	Negative
16	Laxmi Patil	38	P27478/14	1189/14	Bleeding PV	Negative
17	Shantabai	40	P27483/14	1243/14	PID	Only Str
18	Shanti	42	P27488/14	1256/14	Fibroid	Negative
19	Laxmibai	45	4843/14	1318/14	Fibroid	Negative
20	Shankuntala	49	D/166/14	1372/14	PID	TIL

21	Marayawwa	35	P27489/14	1389/14	PID	Negative
22	Kasturibai	50	4992/14	1408/14	DUB with Adenomyosis	Negative
23	Rukmani	50	5703/14	1404/14	Endometrial hyperplasia with DUB	Only Str
24	Mahadevi	45	P27512/14	1473/14	DUB	Negative
25	Parwati	37	P27526/14	1502/14	PID	Negative
26	Rehmanbee	28	P27535/14	1556/14	DUB	Only Str
27	Yallakka	45	P27551/14	1631/14	PID	Only Str
28	Murtuzbee	45	P27552/14	1689/14	Fibroid	TIL
29	Renuka	30	P27553/14	1724/14	PID	Negative
30	Sarojani	44	P27555/14	1789/14	PID	Negative
31	Mahananda	35	P27561/14	1814/14	PID	Negative
32	Laxmibai	40	P27584/14	1863/14	Fibroid	Only Str
33	Lalita	50	P27586/14	1987/14	? Endometrial carcinoma	Only Str
34	Shobha	35	P27587/14	2014/14	Bleeding PV	Negative
35	Anasuyya	48	D/175/14	2146/14	DUB	Only Str
36	Kamala	48	D/177/14	2283/14	PID	Negative
37	Basalingamma	55	449/14	2353/14	Fibroid	Only Str
38	Shanta	49	560/14	2533/14	Chronic cervicitis	Negative
39	Mahananda	40	13416/14	2763/14	DUB	Negative
40	Baby	46	D/186/14	2824/14	Fibroid	Negative
41	Geeta	46	13374/14	2827/14	Fibroid	TIL
42	Bhagawwa	47	191/14	3186/14	PID	Negative
43	Sunanda	40	15891/14	3209/14	Fibroid with PID	Negative

44	Shridevi	30	18780/14	3417/14	DUB	Negative
45	Sona	30	19410/14	3820/14	Multiple fibroid	Negative
46	Laxmi	32	232264/14	4007/14	PID	Only Str
47	Shivakka	46	P27591/14	4276/14	Fibroid	Negative
48	Janaki	43	1224/14	4481/14	PID	Negative
49	Shantawwa	50	296552/14	4890/14	DUB	Only Str
50	Mahadevi	48	3495/14	5756/14	Fibroid	Negative
51	Sumangala	52	362807/14	5911/14	Endometrial hyperplasia/? Carcinoma	Negative
52	Kalavati	47	38092/14	6850/14	Fibroid	Only Str
53	Laxmi	45	2951/15	286/15	PID	Negative
54	Archana	39	2052/15	764/15	? Carcinoma cervix	Negative
55	Sunanda	48	157434/15	2613/15	PID	Only Str
56	Nilamma	41	12006/15	2632/15	DUB	Negative
57	Jayashree	45	13794/15	2634/15	Fibroid	Negative
58	Parvati	44	13063/15	2635/15	PID	Negative
59	Rajeshwari	40	166767/15	2811/15	DUB	Negative
60	Zanathbee	60	166765/15	2814/15	Fibroid	Negative