"EFFECTIVENESS OF RISK OF MALIGNANCY INDEX (RMI) TO DIFFERENTIATE BENIGN FROM MALIGNANT OVARIAN MASSES – A CROSS SECTIONAL STUDY"

REG NO.BJ0111005

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

MASTER OF SURGERY
IN
OBSTETRICS AND GYNAECOLOGY

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA.

APRIL - 2014

KLE UNIVERSITY, BELGAUM,

KARNATAKA

Endorsement By The Hod/Principal/ Head Of The Institution

This is to certify that the dissertation entitled **"EFFECTIVENESS OF RISK OF MALIGNANCY INDEX (RMI) TO DIFFERENTIATE BENIGN FROM MALIGNANT OVARIAN MASSES – A CROSS SECTIONAL STUDY"** is a bonafide research work done by **REG NO.BJ0111005.**

Dr. B.R.DESAI **MD**
Professor and Head,
Department of OBSTETRICS AND GYNAECOLOGY.
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. A. S. GODHI **MS,FICS**
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

ABBREVIATIONS

M	-Menopausal status
RMI	-Risk of Malignancy Index
SD	-Standard deviation
USG	-Ultrasonography
U	-Ultrasound score
PPV	-Positive predictive value.
NPV	-Negative predictive value

ABSTRACT:

Introduction: Diagnostic dilemma exists in differentiating benign from malignant ovarian lesions making treatment difficult. CA125, USG scoring have been used for differentiating these lesions, however significant overlap exist in these test. RMI is a simple, cost-effective method that can be used by gynecologist even at less specialized center to differentiate malignant from benign ovarian masses.

Material& Methods: One year cross sectional study involving ovarian lesions on sonography were analysed in KLE's Dr P.K hospital & MRC in Belgaum. During the study 74 women satisfied the selection criteria, however 10 women were not operated hence only 64 cases were finally analysed . RMI was calculated by combining USG score, CA125 and Menopausal status i.e.

(RMI = U×CA125 ×M) where cut-off value of ≥200 as malignant and finally compared with gold standard HPR .

Statistical analysis: Sensitivity, specificity, positive and negative predictive value was calculated to predict the effectiveness of the RMI.

Results: Out of 64 cases analysed 20 had RMI of ≥200 of which 14 cases were malignant and 6 were benign on HPR. And 44 cases who had RMI <200 out of which only 1 turned out to malignant on HPR.

The sensitivity is 93.3%, specificity is 87.7%, PPV is 70%, and NPV is 97.7%.

Conclusions: The RMI was accurate in differentiating benign from malignant ovarian lesions in majority of the cases. Since the RMI is high there is also a potential role in selection of cases for conservative management or minimal invasive surgery.

Key Words: RMI, OVARIAN TUMOURS, OVARIAN CANCER, USG score,

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

Ovarian tumors frequently present as adnexal masses and are quiet frequent reasons for referral to gynecologist.

Ovarian cancer is the leading cause of death in women with female genital cancers in developing countries. A woman's lifetime risk has been estimated to be about 1 in 55, which represents an increase from the 1970 figure of 1 in 70 (Piver et al., 1996).[1] In the year 2005, an estimated 22,220 new cases of ovarian cancer were diagnosed in the US alone, with 16,210 deaths predicted (Jemal et al., 2005).[2]

Prior to surgery and Histopathological reporting, it is very difficult to differentiate benign from malignant ovarian lesions. 39-69% of the ovarian masses diagnosed after menopause are malignant as compared to 21-24% prior to menopause.[3]

Ovarian cancer is a disease with a poor prognosis. Women commonly have diagnoses of stage III and IV disease, for which 5-year survival rates are around 27% and 16%, respectively.[3]

It has been the hope that early detection of early-stage disease could have a positive impact on the prognosis of this dreaded disease. There has been no universally available test with high sensitivity and specificity for ovarian cancer.

Upto 70% of the ovarian cancers are detected at advance stages because of its bizarre and atypical behavior like abdominal bloating, pain, indigestion, urinary frequency and constipation. Thus a high index of suspicion is required for diagnosis of ovarian cancer.[3]

The prognosis worsens with the late diagnosis. With advanced ovarian disease the mortality rate increases to 70% within 2 years and 90% within 5 years.[3] Pre-operative assessment of adnexal mass/ovarian lesions is thus a challenge for gynecologist. This encouraged us to research on ovarian lesions.

The quality of primary cytoreductive surgery is one of the most important prognostic factors. The extent of cytoreductive surgery is associated with the specific skills and experience of well-trained gynecologic oncologists. The discrimination between benign and malignant ovarian masses is thus important in selective referral of relevant patients to specialized cancer centers (Soegaard et al., 2003).[4]

Until currently, there has been no effective screening method for ovarian cancer and because the lesions are usually asymptomatic until they have metastasized, patients have advanced disease at diagnosis in more than two-thirds of the cases and the prognosis is therefore poor. Several attempts have been made to distinguish benign from malignant conditions.

At the present, one clinical feature provides inadequate performance in discriminating benign and malignant ovarian tumor. For ultrasonographic techniques, the sensitivity and specificity in diagnosis of malignant condition were 62% and 73%, respectively (Morgante et al., 1999; Leelahakorn et al., 2005).[5,6] Serum CA 125 is another promising tool. Elevation of serum CA 125 concentrations is documented in 85% of epithelial ovarian cancers (Benjapibal et al., 2007;Leelahakorn et al., 2005).[6,7] At the cut-off level of 35 U/ml, the sensitivity was 83.1%; but specificity was only 39.3% (Benjapibal et al.,2007).[7] The risk of malignancy index (RMI) is a scoring system of the combination of various clinical features. It has been developed to improve diagnostic accuracy for ovarian malignancy. Jacob et al. (1990) originally

developed the RMI based on ultrasonographic findings, menopausal status, and serum levels of CA 125.[8] By using the RMI at a cut-of level of 200 to indicate malignancy, so called RMI 1, sensitivity and specificity were 85.4% and 96.9%, respectively (Jacobs et al., 1990).[8] Tingulstad et al. (1996) then developed RMI 2. A direct comparison showed that RMI 2 was significantly better at predicting malignancy than RMI 1 (p value < 0.001). The RMI 2 gave sensitivity of 80%, specificity of 92% and positive predictive value (PPV) of 83% while RMI 1 gave sensitivity of 71%, specificity of 96%, and PPV of 89%.[9] It is a simple and cost effective method and can be used by gynecologist even at less specialized centres to diagnose benign and malignant ovarian lesions.

Considering the high burden of the disease and diagnostic difficulties in differentiating benign and malignant lesions the present study was planned to assess the diagnostic value of RMI in discriminating benign from malignant ovarian diseases.

OBJECTIVES

The objective of this study was to assess the diagnostic value of RMI in discriminating benign from malignant ovarian diseases.

REVIEW OF LITERATURE

Ovarian cancer is the most lethal gynecologic malignancy. Ovarian cancer is the third most common cancer of the reproductive organs among women in India [10].

Historical perspectives

The comments on ovarian pathology were made by legendary figures of earlier times as Giovanni Battista Morgagni and Mathew Baillie.

In 1809 Dr. Ephraim McDowell of Kentucky became the first surgeon worldwide successfully to perform ovariotomy. According to a paper on epithelial ovarian tumors written by Heinrich Waldeyer in 1870 suggested a histogenesis similar to that which is now widely accepted for the most common form of ovarian tumor.[11]

Robert Meyer, recognized Brenner tumor as a distinctive neoplasm and also proposed the first classification of sertoli-leydig cell tumors.[12] McNaughten Jones in 1889.[11] first recorded the tumour described by Brenner (1907)

Howard C. Taylor expanded on the concept of tumors intermediate in behaviour between benign and malignant and wrote a significant paper on borderline ovarian tumors.[11]

Schiller made important contribution on dysgerminoma in 1934 and established the Yolk Sac tumor as a distinctive variant of primitive germ cell tumor. He also wrote papers on the localization of alpha-fetoprotein in the tumor cells and relating the morphology of the tumor to alpha-fetoprotein production.[12]

In 1994, Parker D (et. al.) demonstrated the relation between CA-125 and survival of the patients.[13] Similarly in 2002, shutter Eltijo M. J. emphasized on a combination of tumor markers instead of using CA-125 alone in the diagnosis of ovarian tumors.[14]

Hellstrom experimentally studied whether HE-4 protein level in serum can be used as a biomarker for ovarian cancer.[14]

Epidemiology

Worldwide

Ovarian cancer is the fifth most common cause of cancer death in women [American Cancer Society, 2003]. It is the third most common gynecological malignancy among women in the western world, hence is the most lethal. Almost 2/3 of the patients present in advanced stage.[15]

The American Cancer Society estimated that there would be 21,880 new cases of ovarian cancer in 2010 and 13,850 deaths from the disease.The 2010 estimates are 21,880 cases and 13,850 deaths. Epithelial ovarian cancer is the eighth most common cancer in women, and uterine (corpus and endometrial) is fourth. The ovaries are the ninth most common site of cancer in women, accounting for approximately 3% of all new cases, but ovarian cancer causes 5% of cancer deaths—more than any other cancer of the female reproductive system. However, during 2001–2005, the incidence of ovarian cancer declined at a rate of 2.4% annually, and the death rate from ovarian cancer has been stable since 1998.[15]

Indian context

Ovarian tumors are one of the major gynecological disease in India. Women of age group 65 years or older are more frequently diagnosed to have been affected by it. While the highest incidence rate that ranges from 51.1 to 54.0 per 1,00,000 population are clustered in age group between 70 to 84 years.[16]

Highest incidence of benign tumor is seen within 20 to 40 years. In a study it was found that 23.5% of ovarian tumors were serous and 24.5% were mucinous. While the incidence of dermoid cyst varied from 5 to 25% of all ovarian neoplasms.[17]

Thus the commonest category of ovarian tumor encountered were epithelial tumors, second commonest being germ cell tumors. The majority of benign neoplasms occurred in reproductive age group as against the malignant neoplasm which occurred in menopausal age.[18] And the incidence of malignancy ranged between 14 to 40%.[19]

Classification of ovarian tumors

The primary purpose of a classification of ovarian neoplasms is to facilitate communication between different workers in the field of ovarian oncology, like surgeon, pathologist, radiologist and epidemiologist.

Until now, there has been no generally agreed basis for such grouping and numerous classifications of ovarian tumors have been proposed.

In 1973 there was a major development in the form of publication of the world health organization (WHO) classification of ovarian tumors, which was purely a morphological classification with each neoplastic entity being defined solely in

histological terms; as such it had no built in theoretical implications though the grouping together of various tumors in terms of their known or presumed common origin does clearly have some histogenetic connotation.[20]

In 1973 the international society of gynecological pathologist agreed to a new classification of ovarian tumors which largely served as the basis for a new World Health Organisation classification (Scully & Sobin 1999).[21]

The terminology used in this new classification was similar to that of 1973. but the term "Common epithelial tumors" was replaced by "Epithelial stromal tumors". The term epithelial stromal tumor indicates that many of these neoplasms particularly adenofibroma contain a neoplastic stromal component.[21]

The new World Health Organisation classification is as follows.

Histological classification of ovarian tumors [21](Scully & Sabin 1999)

I. Surface epithelial stromal tumors

a. ***Serous tumors***

i. *Benign*

1. Cystadenoma and papillary cystadenoma
2. Surface papilloma
3. Adenofibroma and cystadenofibroma

ii. *Of borderline malignancy (of malignant potential)*

1. Cystadenoma and papillary cystadenoma
2. Surface papilloma
3. Adenofibroma and cystadenofibroma

iii. Malignant

1. Adenocarcinoma, papillary adenocarcinoma and papillary cystadenocarcinoma.
2. Surface papillary adenocarcinoma
3. Malignant adenocarcinoma and cystadenofibroma

b. ***Mucinous tumors, end cervical like and intestinal types***

i. Benign

1. Cystadenoma
2. Adenofibroma and cystadenofibroma

ii. Of borderline malignancy (of malignant potential)

1. Cystic tumor
2. Adenofibroma and cystadenofibroma

iii. Malignant

1. Adenocarcinoma, and cystadenocarcinoma.
2. Malignant adenofibroma and cystadenofibroma

c. ***Endometroid tumors***

i. Benign

1. Cystadenoma
2. Cystadenoma with squamous differentiation
3. Adenofibroma, cystadenofibroma
4. Adenofibroma and cystadenofibroma with squamous differentiation.

ii. Of borderline malignancy (of malignant potential)

1. Cystic tumor
2. Cystic tumor with squamous differentiation
3. Adenofibroma, cystadenofibroma

4. Adenofibroma and cystadenofibroma with squamous differentiation.

iii. Malignant

1. Adenocarcinoma, cystadenocarcinoma.
2. Adenocarcinoma, cystadenocarcinoma with squamous differentiation.
3. Malignant adenofibroma and cystadenofibroma with squamous differentiation.

iv. Epithelial stromal and stromal

1. Adenosarcoma
2. Carcinosarcoma (malignant mesodermal mixed tumor)
3. Stromal sacroma

d. ***Clear cell tumors***

i. Benign

1. Cystadenoma
2. Adenofibroma, Cystadenofibroma

ii. Of borderline malignancy (of malignant potential)

1. Cystic tumor
2. Adenofibroma, cystadenofibroma

iii. Malignant

1. Adenocarcinoma.
2. Malignant adenofibroma and cystadenofibroma

e. ***Transitional Cell Tumors***

i. Brenner tumor

ii. Brenner tumor of borderline malignancy (Proliferating)

iii. Transitional cell carcinoma (Non-Brenner Type)

f. ***Squamous Cell Tumors***

g. ***Mixed epithelial tumors***

i. *Benign*

ii. *Or borderline malignancy*

iii. *Malignant*

h. ***Undifferentiated carcinoma***

II. SEX CORD STROMAL TUMORS

a. ***Granulosa Stromal cell tumors***

i. *Granulosa cell tumor*

1. Adult
2. Juvenile

b. *Thecoma-Fibroma Group*

i. Thecoma

1. Typical
2. Luteinized

ii. Fibroma

iii. Cellular fibroma

iv. Fibrosarcoma

v. Stromal tumor with minor sex-cord element.

vi. Sclerosing stromal tumor

vii. Stromal luteoma

viii. Unclassified

ix. Others

c. *Sertoli-Stromal cell tumors; Androblastomas*

i. Well differentiated

1. Sertoli cell tumor (tubular androblastoma)

2. Sertoli-leydig cell tumor
3. Leydig cell tumor

ii. Sertoli-Leydig cell tumor of intermediate differentiation

1. Variant – with heterologous elements

iii. Sertoli-Leydig cell tumor, poorly differentiated

1. Variant – with heterologous elements

iv. Retiform

1. Variant – with heterologous elements

d. Sex-cord tumor with annular tubules

e. Gynandroblastoma

f. Unclassified

III. GERM CELL TUMORS

a. ***Dysgerminoma***

i. Variant – with syncytiotrophoblast cells

b. Yolk Sac Tumor

i. Variants

1. Polyvesicular vitelline tumor
2. Hepatoid
3. Glandular

c. Embryonal carcinoma

d. Polyembryoma

e. Choriocarcinoma

f. Teratomas

i. Immature

ii. Mature

1. Solid
2. Cystic
3. With secondary tumor
4. Fetiform

iii. *Monodermal*

1. Struma ovarii
    - Variant with secondary tumor
2. Carcinoid tumor
    - Insular
    - Trabecular
3. Strumal carcinoid tumor
4. Goblet cell carcinoid tumor
5. Neuroectodermal tumors
6. Sebaceous tumors
7. Others

IV. GONADOBLASTOMA

a. Variant – with Dysgerminoma or other germ cell tumor

V. GERM CELL SEX CORD STROMAL TUMOR OF NON GONADOBLASTOMA TYPE

a. Variant – with Dysgerminoma or other germ cell tumor

VI. TUMORS OF RETE OVARII

a. Adenoma

i. Cystadenoma

b. Adenocarcinoma

VII. MESOTHELIAL TUMORS

a. Adenomatoid tumor

b. Mesothelioma

VIII. TUMORS OF UNCERTAIN ORGIN AND MISCELLANEOUS TUMORS

a. Small cell carcinoma

b. Tumor of probable Wolffian origin

c. Hepatoid carcinoma

d. Myxoma

e. Others

IX. GESTATIONAL TROPHOBLASTIC DISEASES

X. SOFT TISSUE TUMORS NOT SPECIFIC TO OVARY

XI. MALIGNANT LYMPHOMAS, LEUKAEMIAS AND PLAMACYTOMAS

XII. UNCLASSIFIED TUMORS

XIII. SECONDARY (METASTATIC) TUMORS

XIV. TUMOR LIKE LESIONS

Incidence of individual ovarian tumors

I. Surface epithelial tumors

In new WHO classification the term "Common epithelial tumors" is replaced by "epithelial stromal tumors". Previously these tumors were grouped into two categories, benign or malignant but after the advent of FIGO and WHO classification a third group has been labeled as tumors of borderline malignancy or carcinoma of low potential.[21]

They are the most common tumors of ovary. Gupta et al in 1986 noted their incidence to be 54 to 70%[22]. In a study conducted by Maheshwari et al in 1994 their incidence was recorded as 65.7% of all ovarian tumors. She also reported that the maximum number of cases were found in third decade of life and presented with abdominal lump (71.9%) and pain abdomen (47.4%).[23]

Classification

The surface epithelial tumors are classified according to the following parameter.

1. Cell type – Serous, mucinous, endometroid, clearcell etc.
2. Pattern of growth – Cystic, solid, papillary.
3. Amount of fibrous stroma.
4. Atypia and invasiveness – Benign, borderline or malignant.

A. SEROUS TUMORS

Serous tumors constitute about 30% of all ovarian tumors making them the single most common group of epithelial tumors. They comprise 22% of benign and nearly 50% of malignant primary tumors of ovary. Of which, 50% are benign, 15% are borderline and 35% are invasive carcinoma.[23]

1. **Benign Serous tumors**:

   They commonly present between 20-50 years of age group. With their peak incidence seen in 3rd and 4th decade of life. Cystadenofibroma occur in perimenopausal and menopausal women.[23]

3. Serous Cystadenocarcinoma

It is the most common primary malignant ovarian tumor constituting 14.71% of all ovarian tumors.[24]

B. MUCINOUS TUMORS

Mucinous tumors are defined as tumors in which the epithelial element includes a prominent component of mucus filled cells. They occur less frequently when compared with the serous types. They comprise 6-25% of ovarian neoplasms. On average 85% of them are benign, 6% are borderline tumors and 9% are malignant.[24]

C. ENDOMETRIOID TUMORS

Sampson in 1920 was the first to describe endometroid tumors in ovary. These tumors have an epithelial component that resemble proliferative, hyperplastic or malignant endometrium.[25]

1. Benign endometroid tumors

These are rare and comprise about 10% of ovarian adenofibromas.

D) Transitional cell tumors

Transitional tumors comprise Brenner tumor and Non-Brenner type transitional cell carcinoma.

Brenner tumor comprise around 2% of all the ovarian tumor.[26]

E) UNDIFFERENTIATED CARCINOMA

Approximately 5% of ovarian cancers are poorly differentiated to classify and are designated as undifferentiated carcinoma and they have the worst prognosis of any type of surface epithelial carcinoma.[27]

II. SEX CORD – STROMAL TUMOR

This group includes those tumors originating from the sex cords, mesenchyme or both of the embryonic gonads. These comprise 5-12% of ovarian neoplasms.

A. GRANULOSA CELL TUMORS

Rokitansky first described them. The tumor shows differentiation towards follicular granulosa cells.[28]

They comprise 1-2% of all ovarian tumors and are the most common malignant sex-cord stromal tumors.

There are two types of granulosa cell tumors: an adult type that occurs mainly in menopausal women and a juvenile type that occurs mainly in children.[28]

II. JUVENILE GRANULOSA CELL TUMOR

It is usually seen in children, average age of patient is 15 years.

B. THECOMA – FIBROMA GROUP

They account for 4% of all ovarian tumor and comprises of 7% of sex-cord-stromal neoplasm. The average patient age is between 50 and 55 years.[29]

ii. Fibroma

Fibroma is a benign tumor composed of fibroblasts and collagen fibers.[28]

It is the most common sex cord-stromal tumor, accounting for 1-5% of ovarian tumor. Fibromas occur invariably after puberty, peri or postmenopausal women are commonly affected.[28]

iii. Sclerosing stromal tumor

It is an uncommon benign tumor that occurs mainly in teenagers and young women in their 20's.

C. SERTOLI-LEYDIG CELL TUMOR

This tumor was first described by Pick in 1905. And it constitutes less than 1% of all ovarian tumors. These tumors occur mainly in young patient but arise occasionally in children and postmenopausal women.[30]

a. Well differentiated (Mayer type 1)

These tumors constitute about 11% of sertoli-leydig cell tumors.

b. Intermediately differentiated (Mayer type 2)

These tumors constitute about 54% of sertoli leydig cell tumors.

c. Poorly differentiated (sarcomatoid, undifferentiated, Mayer type 3)

They form 13% of sertoli leydig cell tumor.

III. GERM CELL TUMORS

The germ cell tumors constitute 15-20% of all ovarian tumors.[31]

a. Teratoma

Teratomas form the commonest group of germ cell tumor in ovarian neoplasm. They constitute 25.96% of all ovarian tumors. Benign teratoma occurs in patients of all ages. The peak incidence is between 20 ad 29 years.[31]

ii. Mature solid teratoma

This is a benign tumor common in adolescent and young age (2nd decade) of life.

iii. Immature teratoma

Immature teratoma is one of the most common malignant germ cell tumors of the ovary, 20-30% of patients with such tumor present at the cancer centers.[31] They occur predominantly in children and in young women. The average age of presentation is around 20 years.

B. Dysgerminoma

Chevot identified this tumor in 1911. It is the most common malignant germ cell tumor of the ovary.[31]

Dysgerminoma is a tumor of children and young women. 90% of the patients are under 30 years of age.

C. Yolk sac (Endodermal sinus) tumor

Schiller in 1939 first described this tumor along with clear cell carcinoma under the heading “mesonephroma ovarii”. Telium is 1949 proposed the name endodermal sinus tumor.[27]

It is a malignant germ cell tumor where there is differentiation into yolk sac structures.[27] It occurs principally in children and young women.

F. Choriocarcinoma

Primary ovarian choriocarcinoma is very rare. It is divided into gestational type that is developing from an ovarian pregnancy and non-gestational type as a form of germ cell neoplasm.[33] And usually occur between 3rd and 4th decade of life.

Tumor markers in ovarian cancer

Tumor markers are the biochemical indicators for the presence of tumor. The term usually refers to a molecule that can be detected in plasma or other body fluids.[34]

None of the tumor markers for ovarian carcinoma is 100% specific or 100% sensitive.[34]

a. Tumor markers for epithelial ovarian cancer.

Bast and colleagues in 1981 first described CA-125, a 200 Kd glycoprotein recognized by the murine monoclonal, antibody OC 125 as a maker for epithelial malignancies. A raised level of antigen was detected in 82% of women with epithelial ovarian cancer.[35]

None of the antigen is specific to ovarian cancer, as raised serum levels may be found is 29% of other cancers (lung, breast pancreas and colorectal) and in 6% of women with non malignant condition such as cirrhosis with ascites, acute pancreatitis, ovarian cysts, endometriosis and pelvic inflammatory disease.[36]

Jacobs and Bast found that about 50% of patients with stage I disease had elevated level of CA-125.[37]

CA-125 levels were raised above 35 U/ml in 78% of women with malignant masses but also in 22% of those with benign masses. The predictive value of CA-125 measurements in postmenopasusal women is little greater and using cut off 65 u/ml for which false positive rate is 8%.[35]

The use of CA-125 in monitoring response to treatment is very helpful as there is always a lack in detecting the disease clinically or radiologically. It is a good prognostic marker for stage I disease where there is doubt about the need for adjuvant therapy.[35]

b. Tumor markers in non epithelial ovarian cancer.

Alpha-fetoprotein and human β chorionic gonadotropin are the best known tumor markers in clinical practice and are invaluable in the diagnosis, treatment and follow-up of ovarian germ cell tumors.[38] Serum placental alkalaine phosphatase and lactate dehydrogenase are also sometimes helpful as markers of dysgerminoma.[39] Inhibin, a polypeptide produced by the granulosa cells of the ovary is elevated in granulosa cell tumors.

Ultrasonographic features of Benign and Malignant ovarian tumours

Ultrasonography is an easily available and accessible non-invasive invaluable diagnostic tool. Its cost is also relatively much less as compared to other imaging modalities like CT scan or MRI. Ultrasonography can therefore be of immense help in detecting and evaluating different types of ovarian tumors.

Ovarian tumor may be cystic or solid and can be benign or malignant.[40] Cystic ovarian masses have a smooth wall, no internal echoes. But they often contain low-level echoes representing blood, pus, or cellular debris.[41] Solid tumors are highly, but irregularly, echogenic masses, with varied pictures of solid-cystic areas, complex masses or truly solid tumors. Presence of papillary excrescences and thick and irregular septae or solid areas are regarded as features suggesting malignant ovarian masses. On the other hand, features like thin wall of the lesion, low echogenicity and smooth inner wall structure were more reliable characteristics in predicting benign tumours.

A specific pathologic diagnosis of teratoma can be made from USG when a highly echogenic focus is demonstrated within the tumour mass. This corresponds to the fat and hair-containing semisolid material that fills many of these teratomas. These lesions are virtually always benign, although in the pathologic literature there are reports that 0.3% to 2.0% may undergo malignant degeneration. Therefore it would be valuable to identify a particular sonographic characteristic that would better distinguish teratoma from malignant disease.[42] Complex ovarian masses are lesions that contain both cystic and solid components and the most common one of these are the dermoid cysts.[43,44] The ultrasound appearance is that of an hyperechoic nodular structure, usually with distal acoustic shadow, situated near the cyst wall.[45,46,47,48] The

shadowing may be caused by a calcification or by a sebum and hair conglomerate.[45,47,48] After puberty both Rokitansky nodule and the acoustic shadow appear in over 70% of the cases. Before puberty the echoic nodule appears in about 40% of cases and the acoustic shadow in only 15 % of the dermoid cysts.[48] The dermoid mesh corresponds to the presence of hair inside the cyst that appears as long echoic lines on ultrasonograhy. In some cases only the contour of the cyst may be seen because of the distal acoustic shadow known as tip of the iceberg sign.[45, 47,48,49,] In 1998 Patel *et al*. described the following ultra- sonographic features as being specific for dermoid cysts: a) the presence of an echogenicity with acoustic shadow, b) diffuse or regional shining echoes, c) hyperechoic lines and dots, and d) the presence of a fluid-fluid level.[50]

RISK OF MALIGNANCY INDEX

Up to 70% of the cases are detected at advanced stages, with increased ovarian disease, in which the mortality rate reaches 70% within two years and 90% within five years, which has encouraged research into ovarian cancer screening methods.[3] However, these are costly methods and, because of their elevated false-positive results, they have been ineffective. Ovarian tumors are presented as adnexal masses which give rise to a number of different benign and malignant conditions. The accurate diagnosis of an adnexal mass is a challenge for the gynecologist, because of its bizarre and atypical behaviour. Preoperative diagnostic procedures that are able to distinguish whether an ovarian neoplasm is malignant or benign, could be useful in planning optimized treatment. Until now, the standard strategy for differential diagnosis has been exploratory laparotomy. On the other hand, detailed analysis of the origin of the pelvic mass has encouraged the use of minimal invasive surgery, such as

laparoscopy or mini-laparotomy, in selected cases. A preoperative suggestion of malignancy can guide the gynecologist to refer women with suspected pelvic masses to an oncological unit for appropriate therapy and optimized debulking.

Several diagnostic methods for pelvic masses have been reported, such as abdominal and transvaginal ultrasonography, three-dimensional ultrasound, color Doppler ultrasonography and tumor markers. However, none of these methods used individually has shown significantly better performance in detecting malignant tumors from clinically restricted ovarian masses. The development of a mathematical formula using a logistic model, incorporating menopausal status, the serum level of a glycoprotein called CA 125 (which is considered to be a tumor marker) and ultrasound findings in a score system, has been described in the literature in the form of different malignancy indexes. These indexes were calculated using a simplified regression equation obtained from the product of the ultrasound findings score, the menopausal status score and the absolute value of CA 125 serum levels.

Jacobs et al. originally developed the risk-of-malignancy index in 1990 and it is termed as RMI 1.[8] Tingulstad et al. developed a risk-of-malignancy index in 1996, known as RMI 2 and in 1999 they modified it to form RMI 3 The difference between the three indices lies in the different scorings of ultrasound findings and menopausal status.[9]

The Risk of Malignancy Index has been evaluated in 16 studies.[51,52,53,54,55] The Risk of Malignancy Index, also referred to as RMI I, uses the product of the serum CA 125 level (U/mL), the ultrasound scan result (expressed as a score of 0, 1, or 3), and the menopausal state (1 if premenopausal and 3 if postmenopausal). The test

results vary between 0 and infinity. Jacobs described a cutoff level of 200, with a sensitivity of 85% and a specificity of 97%.

However, most studies evaluate a range of cutoff levels varying between 25 and 250. When 200 was used as cutoff level, the pooled estimate for sensitivity was 78% for a specificity of 87% At a cutoff level of 50, the pooled estimate for sensitivity was 91% for a specificity of 74%.[56,57,58,59.]

In 1996, Tingulstad described an adjustment of the Risk of Malignancy Index, named RMI II. Which is based on the same product as RMI I except that the score for menopause is 1 for premenopausal status and 4 for postmenopausal status and the ultrasound score is expressed as 1 or 4. The score of RMI II varies between 1 and infinity. RMI II is evaluated in seven studies. When 200 was used as cutoff level, the pooled estimate for sensitivity was 79% for a specificity of 81%.[52,60,61,62.]

Finally, an RMI III and RMI IV also have been developed.[9] RMI III and RMI IV both apply different ultrasound scores compared with RMI I and RMI II. RMI III is evaluated in one study and showed at validation a sensitivity and specificity of 74% and 91%, respectively. RMI IV has not been validated in other studies. Tailor's model is based on logistic regression analysis and integrates age, Doppler (ie, time-averaged maximum mean velocity), and a papillary projections score as variables. This model has been evaluated in six publications.[52,63] The score varies between 0 and 100%, and the cutoff level is set at 50%.When 50 was used as cutoff level, the pooled estimate for sensitivity was 60% (95% CI 20–100%) for a specificity of 93% (95% CI 82–100%).When 25 was used as the cutoff level, the pooled estimate for sensitivity was 78% (95% CI 33–100%) for a specifity of 77% (95% CI 35–100%).[52]

All indices presented a significantly better performance in diagnosing malignancy than did each predictor taken separately. These indices were tested by Morgante et al.[5] on another population with evident malignant criteria in the ultrasonography, such as hepatic or distant metastasis, and they found that the RMI 2 performed better for detecting ovarian malignancy.

RMI combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U).[8] The RMI is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml).

RMI = U x M x CA125

- The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions. U = 0 (for an ultrasound score of 0), U = 1 (for an ultrasound score of 1), U = 3 (for an ultrasound score of ≥ 2).
- The menopausal status is scored as 1 = pre-menopausal and 3 = post-menopausal
- The classification of 'post-menopausal' is a woman who has had no menstrual cycle for a period of more than 1 year or a woman who has undergone hysterectomy.
- Serum CA125 is measured in IU/ml and can vary between 0 and hundreds or even thousands of units.

<u>RMI 1.</u>

- Ultrasound score of 0 considered as U = 0, a score of 1 considered as U = 1, and a score of 2 considered as U = 3.

- Premenopausal status considered as M = 1 and postmenopausal status considered as M = 3.
- The serum level of CA125 was used directly in the calculation.[8]

RMI 2

- Ultrasound score of 0 or 1 considered as U = 1, and a score of 2 considered as U = 4.
- Premenopausal status considered as M = 1 and postmenopausal status considered as M = 4.
- The serum level of CA125 was used directly in the calculation. [9]

RMI 3

- Ultrasound score of 0 or 1 considered as U = 1, and a score of 2 considered as U = 3. Premenopausal status considered as M = 1 and postmenopausal status considered as M = 3.
- The serum CA125 level was used directly in the calculation. [9]

The risk-of- malignancy index is apparently able to identify the probability of malignant pelvic masses, by incorporating serum CA 125 serum levels, ultrasound morphology and menopausal status, performed individually in women with ovarian masses. The main purpose of this study was the evaluation of a risk-of-malignancy index defined in a selected population of apparently early lesions. This index is a simple score system which can be applied directly to clinical practice and might be of value in the preoperative assessment of the adnexal mass. It showed itself useful in referring patients with advanced neoplasia to a more complex healthcare unit,

although it does not seem to show prognostic value. However, the performance of the present index must be evaluated in other studies, using a validation sample from a similar population.

In women without evidence of advanced-stage ovarian cancer, the current risk-of-malignancy index is useful in clinical practice for differentiating malignant from benign pelvic masses, as compared to each individual component measured separately. In the present population, this index was more accurate in comparison with the best individual predictor and CA 125 serum level. No increase in the accuracy was observed when analyzed with patients' ages, tumor measurements or bilaterally. The validity of the index depends on the proportions of malignant neoplasm and benign processes and the proportions of initial and advanced stages.

A prospective study was conducted in 1990 in London on 143 patients to assess the risk of malignancy index incorporating CA-125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Each criteria used alone provided statistically significant discrimination. Serum CA125 level of 30units/ml having sensitivity 81% and specificity 75%.An ultrasound score of >3 had a sensitivity of 96.8% and specificity of 77% for malignant ovarian lesion. Sensitive and Specific methods for Pre operative diagnosis provide a rational basis of referral before diagnostic laparotomy. Combining three criteria serum Ca125 level, ultrasound score and menopausal status gives RISK OF MALIGNANCY INDEX (RMI) that is more effective in discriminating between malignant and benign lesion as compared to individual methods statistically.[8]

Using a RMI cut off level of 200 the sensitivity was 85% and specificity was 97%. Patients with RMI score greater than 200 had, on average, 42 times the

background risk of malignancy and those with lower values had, 0.15 times the background risk. [8]

A prospective study was conducted in 173 women in Norway for evaluation of a risk of malignancy index based on serum CA 125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. Using a RMI cut off level of 200 to indicate malignancy, it gave a sensitivity of 80%, specificity 92% and PPV of 83%.[9]

Another similar cross sectional study was done on 158 women in Brazil between 1996-1998.The best individual performance was found in CA 125 sensitivity of 78%, specificity of 75%. Followed by ultrasound score sensitivity 75% and specificity 73% and menopausal status sensitivity 73% and specificity 69% The performance obtained for RMI at cut off level 150 was sensitivity and specificity of 79%.[64]

A study evaluated the ability of RMI to discriminate benign from malignant pelvic masses in 140 women between January 1998 and June 1999. Using an RMI cutoff level of 200 to indicate malignancy, the RMI derived from this data set gave a sensitivity of 87.3%, a specificity of 84.4%, and a positive predictive value of 82.1%. The study concluded that, RMI is able to correctly discriminate malignant from benign pelvic mass. It can be introduced easily into clinical practice to facilitate the selection of patients for primary surgery.[65]

A study to evaluate the ability of RMI to discriminate between benign and borderline or malignant ovarian tumor enrolled 209 women with pelvic masses admitted for laparotomy between January 2002 and December 2007. Using a cut-off level of 200 to indicate malignancy, the RMI 1 gave sensitivity of 70.6%, specificity

of 83.9%, PPV of 75%, and NPV of 80.6%. The RMI 2 gave sensitivity of 80%, specificity of 78.2%, PPV of 71.6%, and NPV of 85.1%. The RMI 2 was significantly better in predicting malignancy than RMI 1. Authors concluded that, the RMI is able to discriminate between benign and borderline or malignant ovarian tumor.[66]

A study aimed to evaluate the use of RMI in primary evaluation of patients with adnexal masses in daily clinical practice recruited 151 women with adnexal masses. Using a cut-off level of 238 to indicate malignancy, the RMI showed a sensitivity of 89.5%, a specificity of 96.2%, a PPV of 77.3%, a NPV of 98.4% and an accuracy of 95.4%. Study concluded that, RMI is a simple, easily applicable method in the primary evaluation of patients with adnexal masses of high risk of malignancy, resulting in timely referal to gynecological oncology centers for suitable surgical operations.[67]

Another study to validate the use of RMI ≥200 as a tool for preoperative identification of ovarian cancer at a tertiary center enrolled 1159 women with pelvic mass. There were 778 women diagnosed with benign pelvic mass, while 251 had ovarian cancer and 74 had borderline ovarian tumor. Fifty-six women were diagnosed with other forms of cancer. Sensitivity and specificity for ovarian cancer vs. benign pelvic mass for RMI ≥200 were 92 and 82%, respectively. Corresponding positive and negative predictive values were 62 and 97%. Authors concluded that, RMI ≥200 is a reliable tool for identifying patients with ovarian cancer or pelvic masses at a tertiary centre to select patients for further preoperative examinations.[68]

METHODOLOGY

The present study was conducted in the Department of Obstetrics and Gynecology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was a one year cross sectional study.

Study duration and period

This one year study was conducted during the period from January 2012 to December 2012.

Place

The present study was conducted at Department of Obstetrics and Gynaecology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a tertiary care hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of data

Women suspected to have ovarian lesions on ultrasonography and who underwent laparotomy for the same were enrolled in the study.

Sample size

A total of 74 women *suspected to have ovarian lesions* were studied.

Sampling procedure

- The sample size was calculated considering the prevalence based on the formula as below. **Sample size** – 64 patients
- Calculated from formula as below
- n=4pq/d2
- Where,

  P = Sensitivity 80%

  q = 100-P

  d = Error 10%
- Hence, 4 × 80 × 20 / 102
- Therefore, n=64
- Hence the sample size of 64 was planned. However during the study period 74 women fulfilled the selection criteria and hence were enrolled in the study.

Selection criteria

Inclusion

- Any ovarian mass suspected on sonography with either one of the parameters above 5 cm.

Exclusion

- Women with previous bilateral salpingoopherectomy
- Women with previously treated carcinoma.

Ethical clearance

The study ethical clearance was obtained from the Institutional Ethical committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

Women fulfilling selection criteria were explained about the nature of the study and a written informed consent was obtained (Annexure I) prior to the enrolment.

Method of collection of data

After the enrollment demographic data and obstetric history were obtained. Further these women were subjected to thorough clinical examination. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The selected women underwent investigations such as serum CA125 and ultrasound. Transabdominal / transvaginal scan was performed by single observer (Sonologist) using the 3.5 Mhz of PHILIPS HD II machine to calculate USG score.

Outcome variables

RMI index

It combines three pre-surgical features viz;

- Serum CA125 (Measured in IU/mL) – May vary between zero and hundreds or even thousands (CA125)
- Menopausal status (M) which is interpreted as
    - 1 = pre-menopausal
    - 3 = post-menopausal
- Ultrasound score (U) – Which is interpreted based on New weighted scoring system (Learner et al)[69]

Parameter	**0**	**1**	**2**	**3**
Wall structure	Smooth/ small irregularites <3mm	-	Solid or non applicable	Papillarities ≥ 3mm
Shadowing	Yes	No	-	-
Septa	None or thin < 3mm	Thick ≥ 3 mm	-	-
Echogenicity	Sonolucent or low level echo or echogenic core	-	-	Mixed or high

Based on the New weighted scoring system the ultrasound score (U) is further interpreted as

- 0 for an ultrasound score of 0
- 1 for an ultrasound score of 1
- 3 for an ultrasound score of ≥ 2

Based on these variables RMI index is calculated as below;

RMI = U x M x CA125

Based on the RMI 1 index values the lesions were interpreted as benign if the RMI score was < 200 and malignant if the score was > 200.

Histopathological report

Ovary tissue specimens were received in 10% formalin. Ovarian tissue was grossly examined first and findings were noted. The laterality, size, consistency, cystic content and presence of solid areas, necrosis, hemorrhage and papillae and any other suspicious appearing areas.

Fixative used for specimen

The fixative used for fixation of tissue was 10% formalin. For fixation, volume of the formalin used was twenty times the volume of the specimen. After receiving the specimen in formalin, assigning the laboratory number was done in all the cases.

Processing of specimen

After fixation tissue was dehydrated by passing the tissue through a series of ascending grades of alcohol.Then clearing was done by passing it through two changes of xylene. Tissue embedding was done in molten paraffin wax. Wax blocks were made using Leuckhart's mould.Thin sections of four microns were cut, slides were prepared and stained by Harris' Haematoxylin and Eosin stain.

Harris'Haematoxylin and Eosin staining procedure:

Solutions:

Differentiating solution

1% acid alcohol

1 mL of concentrated HCL

100 mL of 70% of ethanol

Scott solution

1 L tap water

10 g magnesium sulphate

2 g sodium bicarbonate

Staining procedure:

1. Deparaffinise the sections and take to water.
2. Stain the section in Harris' Haematoxylin (Sigma) for two minutes thirty seconds.

3. Rinse in running tap water.
4. Differentiate in 1%acid alcohol 1-6 dips.
5. Rinse in running tap water.
6. Blue in Scott's tap water substitute solution for 5 seconds to 2 minutes.
7. 95%ethanol.
8. Alcoholic Eosin Y for 30 seconds.
9. 100% ethanol 5 dips x 3 changes.
10. Clear in xylene and mount with DPX (Di Butyl Pthylate Xylene).

H and E stained sections were examined microscopically and histologic interpretation was done.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and proportions and continuous data was expressed as mean ± standard deviation (SD). The categorical data was analysed using chi-square test The accuracy of RMI in differentiating benign and malignant lesions was determined by sensitivity, specificity, positive predictive value and negative predictive value. Kappa agreement was used to correlate the agreements. A 'p' value of less than or equal to 0.05 was considered as statistically significant.

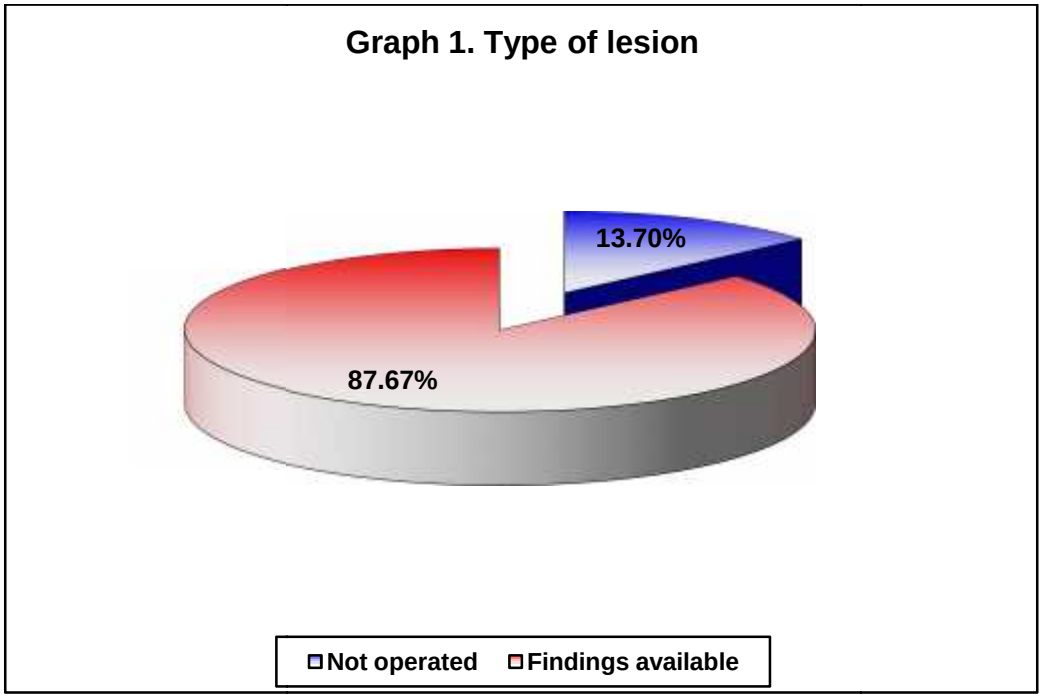
RESULTS

This one year cross sectional study was conducted in the Department of Obstetrics and Gynecology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 74 women suspected to have ovarian lesions were studied from January 2012 to December 2012.

The data obtained was coded and entered into the master chart (Annexure IV). The data was analysed and the final observations were tabulated as below.

Table 1. Total number of cases

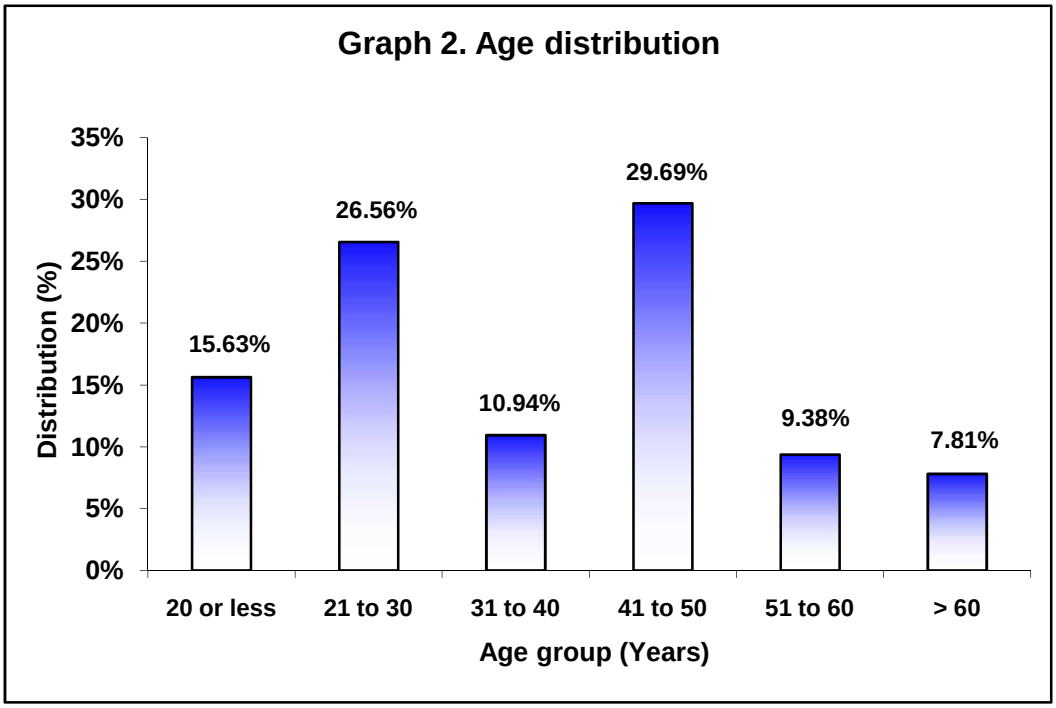
Type	Distribution (n=74)	
	Number	Percentage
Not operated	10	13.70
Findings available	64	87.67
Total	**74**	**100.00**



In the present study of the 74 women, 10 (13.51%) were not operated and in the remaining 64 (87.67%) the histopathological reports were available. Hence 64 cases were studied.

Table 2. Age distribution

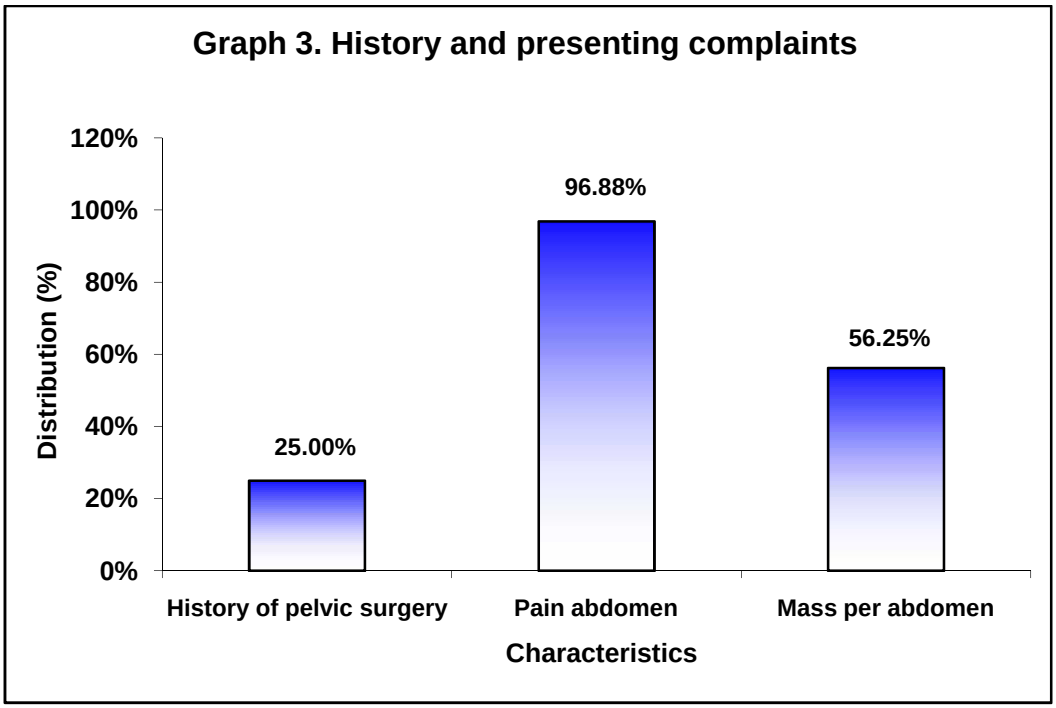
Age group (Years)	Distribution (n=64)	
	Number	**Percentage**
20 or less	10	15.63
21 to 30	17	26.56
31 to 40	7	10.94
41 to 50	19	29.69
51 to 60	6	9.38
> 60	5	7.81
Total	**64**	**100.00**



In the present study 26.56% of the women presented with age between 21 to 30 years and 29.69% between 41 to 50 years. The mean age of the study population was 38.41 ± 15.71 years.

Table 3. History and presenting complaints

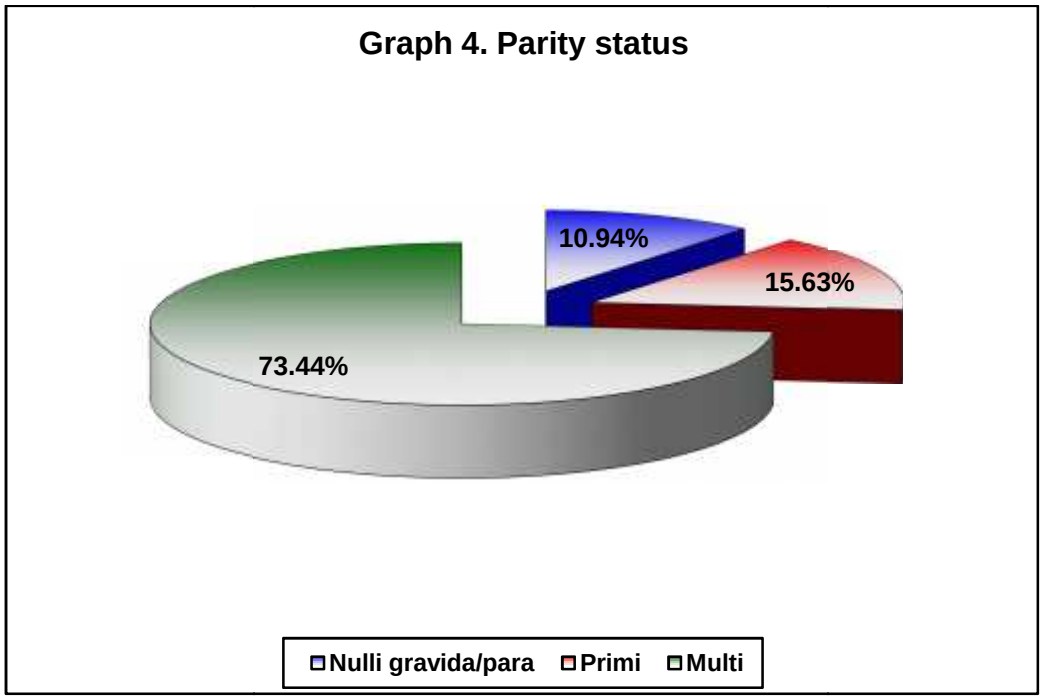
Characteristics	Distribution (n=64)	
	Number	Percentage
History of pelvic surgery	16	25.00
Pain abdomen	62	96.88
Mass per abdomen	36	56.25



In this study of the 64 women studied, 96.88% of the women presented with pain abdomen and 56.25% with mass per abdomen. The history of pelvic surgery was noted in 25% of the women.

Table 4. Parity status

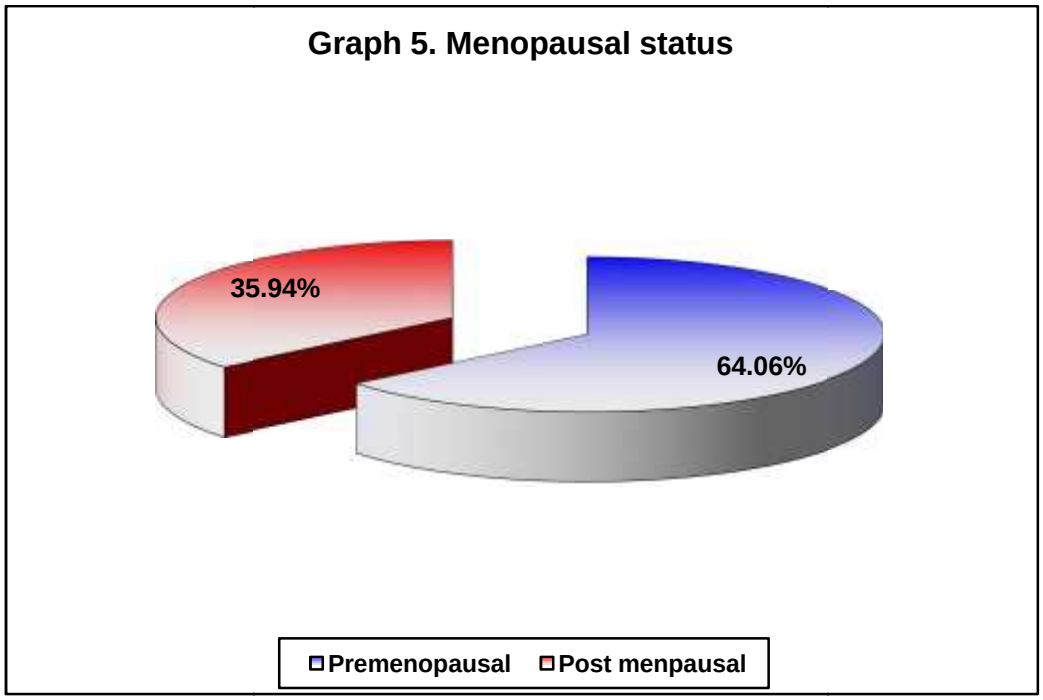
Parity	Distribution (n=64)	
	Number	**Percentage**
Nulli gravida / para	7	10.94
Primi	10	15.63
Multi	47	73.44
Total	**64**	**100.00**



In this study most of the women (73.44%) reported multi parity while 15.63% were primiparous.

Table 5. Menopausal status

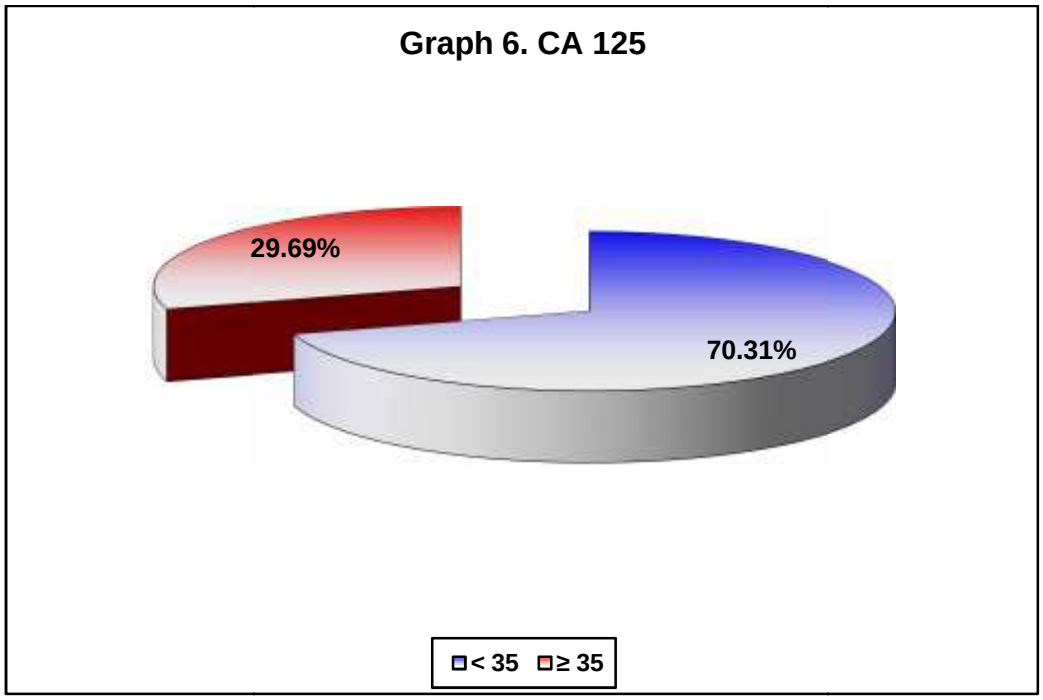
Menopause	Distribution (n=64)	
	Number	Percentage
Premenopausal	41	64.06
Post menopausal	23	35.94
Total	**64**	**100.00**



In the present study 64.06% of the women presented with pre menopausal status while 35.94% reported post menopausal state.

Table 6. CA 125

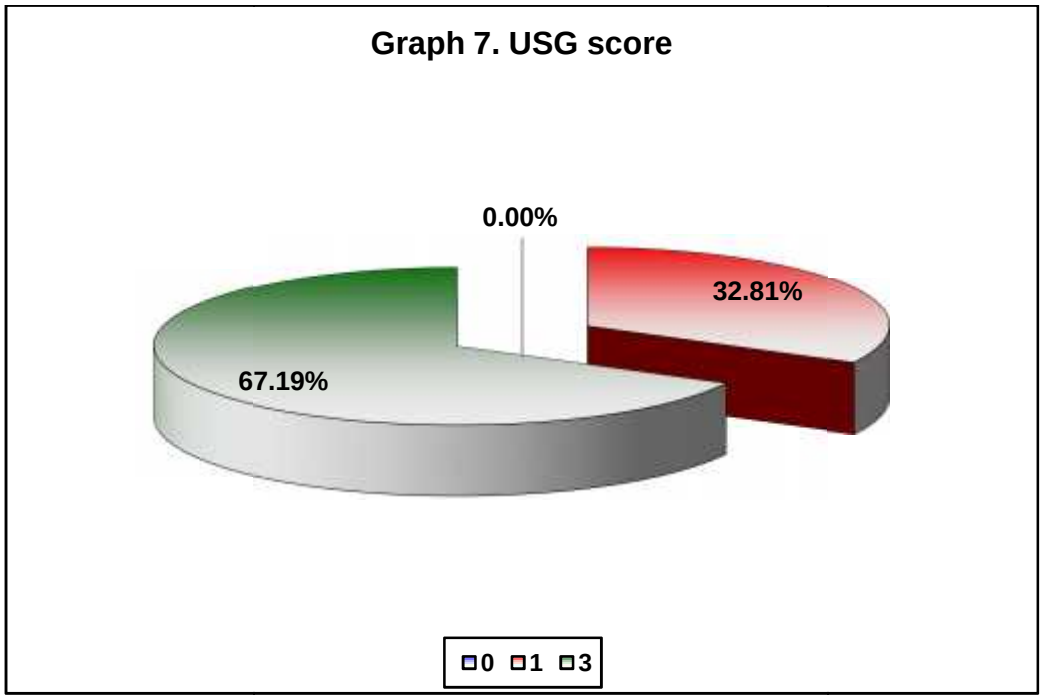
CA 125 levels (IU/mL)	Distribution (n=64)	
	Number	**Percentage**
< 35	45	70.31
≥ 35	19	29.69
Total	**64**	**100.00**



In this study 70.31% of the women had serum CA 125 levels of < 35 while 29.69% had ≥ 35. The mean serum CA125 levels were 178.10 ± 646.56.

Table 7. USG score

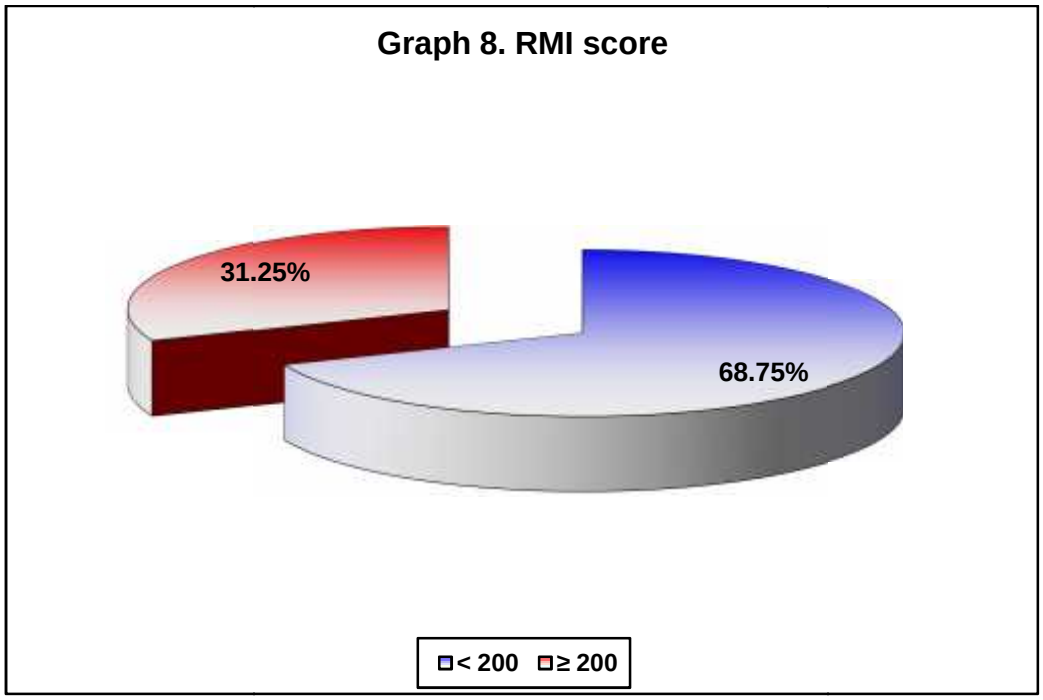
USG score	Distribution (n=64)	
	Number	**Percentage**
0	0	0.00
1	21	32.81
3	43	67.19
Total	**64**	**100.00**



In the present study the USG score of one was noted in 32.81% of the women while 67.19% had USG score of three. The mean USG score of the study population was 3.08 ± 2.32.

Table 8. RMI score

RMI Score	Distribution (n=64)	
	Number	**Percentage**
< 200	44	68.75
≥ 200	20	31.25
Total	**64**	**100.00**

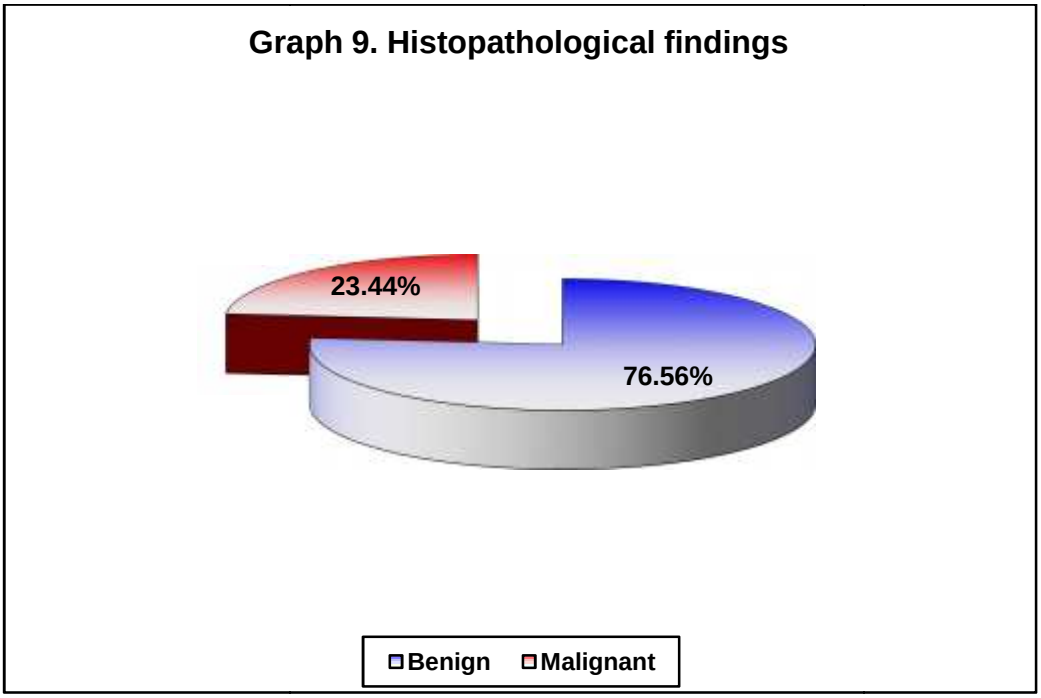


In this study RMI score was found to be <200 in 68.75% of the women and in 31.25% of the women it was ≥ 200. The mean RMI scores were 1485.48 ± 5835.41.

Table 9. Histopathological findings

Findings	Distribution (n=64)	
	Number	**Percentage**
Benign	49	76.56
Malignant	15	23.44
Total	**64**	**100.00**

Graph 9. Histopathological findings



In the present study the histopathological reports showed benign lesions in 76.56% of the women while in 23.44% of the women malignant lesions were noted.

Table 10. Histopathological findings – Benign lesions

Benign lesions	Distribution (n=49)	
	Number	**Percentage**
Serous cystadenoma	12	24.49
Mucinous cystadenoma	11	22.45
Serous cyst	5	10.20
Ovarian serous cyst	3	6.12
Ovarian haemorrhagic cyst	3	6.12
Simple cyst	2	4.08
Dermoid cyst	2	4.08
Ovarian dermoid cyst	2	4.08
Ovarian cystadenofibroma	1	2.04
Ovarian mucinous cystadenoma	1	2.04
Mesenteric tumour	1	2.04
Ovarian serouscystadenoma	1	2.04
Ovarian simple cyst	1	2.04
Papillary serous cystadenoma	1	2.04
Mass of unknown origin	1	2.04
Mixed serous and mucinous cystadenoma	1	2.04
Granulosa cell tumor	1	2.04
Total	**49**	**100.00**

In the present study the commonest diagnosis in the benign lesions was serous cystadenoma in (24.49%) while mucinous cystadenoma was noted in 22.45% of the women. The distribution of other lesions is as shown in table 9.

Table 11. Histopathological findings – Malignant lesions

Malignant lesions	Distribution (n=15)	
	Number	**Percentage**
Papillary adenocarcinoma	3	20.00
Mucinous cystadenocarcinoma	2	13.33
Ovarian adenocarcinoma	2	13.33
Serous papillary adenocarcinoma	2	13.33
Ovarian papillary serous tumor	1	6.67
Ovarian serous adenocarcinoma	1	6.67
Brenner tumor	1	6.67
Ovarian dysgerminoma	1	6.67
Tube adenocarcinoma	1	6.67
Yolksac tumor	1	6.67
Total	**15**	**100.00**

In the present study the commonest diagnosis in the malignant lesions included papillary adenocarcinoma (20%) and, mucinous cystadenoma carcnoma, ovarian adenocarcinoma and serous papillary adenocarcinoma (13.33% each). The distribution of other malignant lesions is as shown in table 10.

Table 12. Comparison of menopausal status and HPR

Menopause	RMI findings				Total	
	≥ 200		< 200			
	No	%	No	%	No	%
Premenopausal	3	7.32	38	92.68	41	100.00
Post menopausal	12	52.17	11	47.83	23	100.00
Total	**15**	**23.44**	**49**	**76.56**	**64**	**100.00**

p < 0.001

In the present study of the 41 women with premenopausal status RMI findings showed 7.32% women with RMI ≥ 200 while 92.68% had RMI score of < 200. This difference was statistically significant (p<0.001).

Table 13. Accuracy of CA 125 in comparison to histopathology

Histopathological report	CA125		Total
	≥ 35	< 35	
Malignant	13	2	15
Benign	6	43	49
Total	19	45	64

Kappa=0.681 **p < 0.001**

Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
86.67	**87.75**	**68.42**	**95.56**

In the present study of the 19 women with CA125 score of ≥ 35, 13 had malignant lesions on histopathology while 6 women had benign lesions. The sensitivity of CA125 in predicting malignant lesions as compared to histopathology was 86.67% with 87.75% specificity.

Table 14. Accuracy of USG scoring in comparison to histopathology

Histopathological report	USG score		Total
	≥ 5	< 5	
Malignant	10	5	15
Benign	10	39	49
Total	20	44	64

p < 0.001

Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
66.66	**79.59**	**50.00**	**88.63**

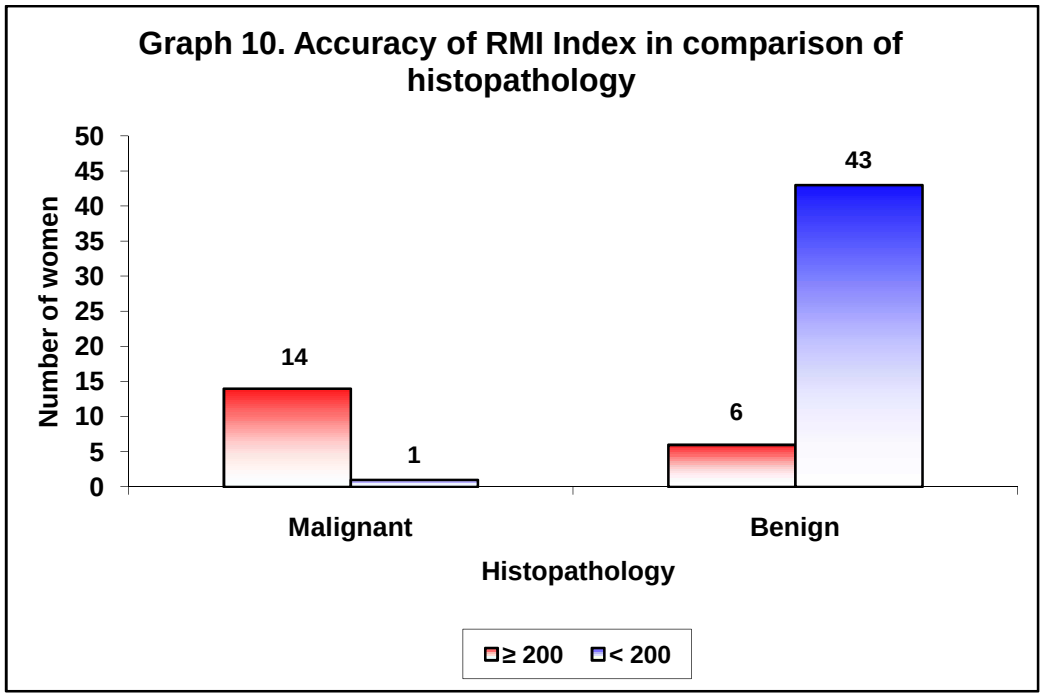
In this study of the 20 women with USG score of ≥ 5, 10 each had malignant and benign lesions on histopathology. The sensitivity of USG score in predicting malignant lesions as compared to histopathology was 66.66% with 79.59% specificity.

Table 15. Accuracy of RMI Index in comparison to histopathology

RMI Index	Histopathology		Total
	Malignant	**Benign**	
≥ 200	14	6	20
< 200	1	43	44
Total	15	49	64

Kappa=0.727 (Substantial agreement) **p < 0.001**

Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
93.33	**87.76**	**70.00**	**97.73**



In the present study of the 15 malignant lesions on histopathology, 14 had RMI score ≥ 200 while 1 women had RMI score of < 200. The sensitivity of RMI in predicting malignant lesions as compared to histopathology was 93.33% with 87.76% of specificity.

DISCUSSION

A pelvic mass is one of the most frequent indications for referral to specialist gynecologists. Often, these pelvic masses are malignant and require surgical treatment. Up to 24% of ovarian tumors in premenopausal women are malignant and up to 60% are malignant in postmenopausal women[8].

The preoperative diagnosis of whether a mass is malignant cannot always be made with current diagnostic modalities. Surgery can be optimally planned if an ovarian neoplasm is known to be benign or malignant in advance. The type of surgical procedure and the experience of the surgeon are important factors for the prognosis of ovarian cancer. An improved method for preoperative discrimination of a pelvic mass would result in more women receiving first-line therapy from appropriately trained and experienced personnel . For such referrals to be efficient, improved specific and sensitive methods for diagnosing ovarian cancers are needed.

Many investigators have employed a variety of sonographic variables in an attempt to predict a malignancy, including Doppler analysis. A number of articles have discussed ovarian tumors and the panel of different tumor markers .Various combined methods for evaluating the risk of ovarian cancer in women have been proposed .

The risk of malignancy index (RMI) is a simple scoring system based on menopausal status, ultrasound, and serum concentrations of CA-125. This has given much better results than a single parameter. The RMI can be applied in less specialized centers.

The present study was aimed to assess the diagnostic value of RMI in discriminating benign from malignant ovarian diseases. This study was conducted on a total of 74 women suspected to have ovarian lesions from January 2012 to December 2012 in the Department of Obstetrics and Gynecology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. Of the 74 women, 10 (13.51%) were not operated and in the remaining 64 (87.67%) the histopathological reports were available. Hence 64 cases were studied.

In this study the commonest age was 41 to 50 years (29.69%) followed by 21 to 30 years (26.56%) and the mean age was found to be 38.41 ± 15.71 years. These results were in agreement with the findings in literature stating that, the ovarian tumors can occur at any age but their peak incidence is in the reproductive age group.

In the present study of the 64 women studied, 96.88% of the women presented with pain abdomen and 56.25% with mass per abdomen. With regard to obstetric history, most of the women (73.44%) reported were multiparous. The history of pelvic surgery was present in 25% of the women.

In the present study almost two thirds of the women (64.06%) reported pre menopausal status followed by post menopausal state (35.94%) The serum CA125 levels were < 35 in 70.31% of the women and 29.69% had ≥ 35 with mean serum CA125 levels being 178.10 ± 646.56. Based on USG findings the score of one was found in 32.81% of the women while 67.19% had USG score of three with mean USG scores being 3.08 ± 2.32.

In this study RMI score was calculated to be <200 in 68.75% of the women and in 31.25% of the women it was ≥ 200. The mean RMI scores were 1485.48 ± 5835.41.

In the present study, 76.56% of the women had benign and 23.44% had malignant lesions. A similar study to verify the effectiveness of the RMI in the discrimination between benign lesions and malignant adnexal masses in clinical practice reported benign tumor in 62.96% and malignant in 37.04% of the patients. Another prospective study from Turkey to evaluate the ability of four risk of malignancy indices (RMI) to detect malignant ovarian tumors on 100 women reported that, 80% had benign and 20% had malignant disease.[62]

In this study, the commonest diagnosis in the benign lesions was serous cystadenoma seen in 24.49% followed by mucinous cystadenoma seen in 22.45% of the women while, the commonest diagnosis in the malignant lesions included papillary adenocarcinoma (20%) and, mucinous cystadenocarcinoma, ovarian adenocarcinoma and serous papillary adenocarcinoma (13.33% each). A prospective study from Turkey also reported mucinous cystadenocarcinoma as the commonest diagnosis in malignant cases (10 out of 20) and endometriosis in benign cases (27 out of 80).[62]

Risk of malignancy index (RMI) is recommended in assessment of patients with adnexal masses. In this study, of the 15 women with malignant lesions on histopathology, 14 women had RMI score ≥ 200 while 1 woman had RMI score of < 200. The sensitivity of RMI in predicting malignant lesions as compared to histopathology was 93.33% with 87.76% of specificity. Also of the 19 women with CA125 score of ≥ 35, 13 had malignant lesions on histopathology while 6 women had

benign lesions. The sensitivity of CA125 in predicting malignant lesions as compared to histopathology was 86.67% with 87.75% specificity. Similarly, of the 20 women with USG score of ≥ 5, 10 each had malignant and benign lesions on histopathology. The sensitivity of USG score in predicting malignant lesions as compared to histopathology was 66.66% with 79.59% specificity.

In the 1990s, Jacobs et al.[8] originally developed the RMI, which is now termed RMI 1. Tingulstad et al.[9] developed their version of the RMI in 1996 and it is known as RMI 2. In 1999, Tingulstad et al.[9] modified the RMI, which is termed RMI 3. Yamamoto et al.[70] created their own model of a malignancy risk index. They added the parameter of the tumor size (S) to the RMI and have termed it the RMI 4. Jacobs et al. originally developed the RMI, and subsequently the same group reproduced the results in a second patient group, establishing the superiority of RMI over the individual parameters[8].

Jacobs et al in his study[8] assessed age, ultrasound score, menopausal status, a clinical impression score and serum CA 125 level to see how they could best distinguish between patients with benign (n=101) and malignant (n=42) pelvic masses. Each criteria used alone provided statistically significant discrimination. The most useful individual criteria were a serum CA 125 level of 30 U/ml (sensitivity 81%, specificity 75%) and an ultrasound score of 2 (sensitivity 71%, specificity 83%). Three criteria could be combined in a risk of malignancy index (RMI) which is simply calculated using the product of the serum CA 125 level (U/ml), the ultrasound scan result (expressed as a score of 0, 1 or 3) and the menopausal status (1 if premenopausal and 3 if postmenopausal). This index was statistically virtually as effective a discriminant between cancer and benign lesions as more formal methods.

Using an RMI cut-off level of 200, the sensitivity was 85% and the specificity was 97%. Patients with an RMI score of greater than 200 had, on average, 42 times the background risk of cancer and those with a lower value 0.15 times the background risk. These findings were comparable with the present study where the sensitivity of RMI in predicting malignant lesions as compared to histopathology was 93.33% with 87.76% of specificity.[9]

Similar results were reported in recent study where sensitivity of RMI was 83.33%, specificity 94.12%, positive predictive value was 89.29% and negative predictive value was 90.57% using RMI cut off value of 200.[9]

The RMI has been evaluated in 16 studies[51,52,53,54,55.] Since its description by Jacobs in 1990 he described a cutoff level of 200, with a sensitivity of 85% and a specificity of 97%.12 However, most studies evaluate a range of cutoff levels varying between 25 and 250. When 200 was used as cutoff level, the pooled estimate for sensitivity was 78% (95% CI 71–85%) for a specificity of 87% (95% CI 83–91%).14–17,20,58–65) At a cutoff level of 50, the pooled estimate for sensitivity was 91% (95% CI 85–97%) for a specificity of 74% (95% CI 69–80%).

In 1996, Tingulstad described an adjustment of the Risk of Malignancy Index, named RMI II which is based on the same product as RMI I except that the score for menopause is 1 for premenopausal status and 4 for postmenopausal status and the ultrasound score is expressed as 1 or 4. The score of RMI II varies between 1 and infinity. RMI II is evaluated in seven studies. When 200 was used as cutoff level, the pooled estimate for sensitivity was 79% (95% CI 71–87%) for a specificity of 81% (95% CI 72–90%).[52,60,61,62.]

Finally, an RMI III and RMI IV also have been developed. RMI III and RMI IV both apply different ultrasound scores compared with RMI I and RMI II. RMI III is evaluated in one study and showed at validation a sensitivity and specificity of 74% and 91%, respectively. RMI IV has not been validated in other studies[70].

In 2001 Manjunath et al. compared RMI 1, RMI 2, and RMI 3 with each other and also confirmed that there was no statistical difference between these three indices in benign - malignancy discrimination. [71]

In a study by Clarke et al. , using a cut-off of 120, found that RMI 1 had a sensitivity of 72% and a specificity of 87%; RMI 2 had a sensitivity of 76% and a specificity of 81%; RMI 3 had a sensitivity of 74% and a specificity of 84%. [72]

In 2009 Yamamoto et al.developed their own RMI by using tumor size and called it RMI 4. Their study confirms that, at a cutoff level of 450, the accuracy of the RMI 4 was better than RMI 1 (p=0.0013), RMI 2 (p=0.0009) and RMI 3 (p=0.0013) with a cutoff level of 200. They observed that at a cutoff level of 450 the sensitivity, specificity, positive predictive value, negative predictive value and accuracy were respectively, 86.8%, 91.0%, 63.5%, 97.5%, and 90.4%.[70]

A review reported that, when the Risk of Malignancy Index was applied with a sensitivity of 78% and a specificity of 87% to a woman with an adnexal mass and a prior probability of disease of 10%, the post test probability for a woman with an Risk of Malignancy Index above the threshold of 200 would have a probability of malignancy of 40%, whereas a woman with an Risk of Malignancy Index below this threshold would have a probability of disease of 2.7%. However it should be consider that this test already combines information on CA 125 level, ultrasound scan result,

and menopausal state, thus limiting the possibility of differentiation of the prior probability of disease. However, a distinction between a probability before surgery of 2.7% compared with 40% is clinically useful.

Overall, the RMI is a simple method that can be used by general gynecologists to aid in selecting a patient for referral to cancer centers for primary surgery.

CONCLUSION

Based on the results of this study which showed the sensitivity of RMI in predicting malignant lesions when compared with histopathology was 93.33% with 87.76% of specificity with PPV of 70% and NPV of 97.73% it may be concluded that, the RMI is a simple scoring system with higher accuracy in differentiating benign from malignant ovarian masses and can be easily introduced in clinical practice and can be the test of choice in the preoperative evaluation of the adnexal mass under primary settings. Also since the RMI is high there is also a potential role in selection of cases for conservative management or minimal invasive surgery.

SUMMARY

The risk of malignancy index (RMI) is a simple scoring system based on menopausal status, ultrasound, and serum concentrations of CA-125. This has given much better results than a single parameter . The RMI can be applied in less specialized centers.

The present study was aimed to assess the diagnostic value of RMI in discriminating benign from malignant ovarian diseases.

This study was conducted on a total of 74 women suspected to have ovarian lesions from January 2012 to December 2012 in the Department of Obstetrics and Gynecology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

In the present study 28.38% of the women presented with age between 21 to 30 years and 24.32% between 41 to 50 years. The mean age of the study population was 38.7 ± 16.0 years.

In this study of the 74 women studied, 93.24% of the women presented with pain abdomen and 48.65% with mass per abdomen. The history of pelvic surgery was noted in 21.62% of the women.

In this study most of the women (70.27%) reported were multi parous while 17.57% were primiparous.

In the present study 63.51% of the women presented with pre menopausal status while 36.49% reported post menopausal state.

In this study 72.97% of the women had serum CA 125 levels of < 35 while 27.03 had ≥ 35. The mean serum CA125 levels were 178.10 ± 646.56.

In the present study the USG score of one was noted in 31.08% of the women while 68.92% had USG score of three. The mean USG score of the study population was 3.08 ± 2.32.

In this study RMI score was found to be <200 in 70.27% of the women and in 29.73% of the women it was ≥ 200. The mean RMI scores were 1485.48 ± 5835.41.

In the present study of the 74 women, 10 (13.51%) were not operated. In the remaining the histopathological reports revealed 66.22% with benign and 20.27% with malignant lesions.

In the present study the commonest diagnosis in the benign lesions was serous cystadenoma in (24.49%) while mucinous cystadenoma was noted in 22.45% of the women. The distribution of other lesions is as shown in table 9.

In the present study the commonest diagnosis in the malignant lesions included papillary adenocarcinoma (20%) and, mucinous cystadenocarcinoma, ovarian adenocarcinoma and serous papillary adenocarcinoma (13.33% each). The distribution of other malignant lesions is as shown in table 10.

In the present study of the 15 malignant lesions on histopathology, 14 had RMI score ≥ 200 while 1 women had RMI score of < 200. The sensitivity of RMI in predicting malignant lesions as compared to histopathology was 93.33% with 87.76% of specificity.

In the present study of the 41 women with premenopausal status RMI findings showed 7.32% women with RMI ≥ 200 while 92.68% had RMI score of < 200. This difference was statistically significant ($p<0.001$).

In the present study of the 19 women with CA125 score of ≥ 35, 13 had malignant lesions on histopathology while 6 women had benign lesions. The sensitivity of CA125 in predicting malignant lesions as compared to histopathology was 86.67% with 87.75% specificity.

In this study of the 20 women with USG score of ≥ 5, 10 each had malignant and benign lesions on histopathology. The sensitivity of USG score in predicting malignant lesions as compared to histopathology was 66.66% with 79.59% specificity.

In the present study of the 20 women with CA125 score ≥ 35, 90% of the women had RMI score of ≥ 200 and 10% had RMI scores of < 200. This difference was statistically significant ($p<0.001$).

In the present study of the 23 women with USG score of ≥ 5, 65.22% of the women had RMI score of ≥ 200 and 34.78% women had RMI scores of < 200. This difference was statistically significant ($p<0.001$).

BIBLIOGRAPHY

1. Piver MS (1996). Prophylactic oophorectomy: reducing the US death rate from epithelial ovarian cancer. A continuing debate. The Oncologist, 1, 326–30.
2. E mal A, Murray T, Ward E, et al (2005). Cancer statistics, 2005. CA: A Cancer Journal for Clinicians, 55, 10–30.
3. Berek & Novak ‘s Text book of Gynecology. (14th edition)
4. Soegaard R, Knudsen A, Rix P, et al. Risk of malignancy Index in the preoperative evaluation of patients with adnexal masses. Gynecol Oncol. 2003;90:109-12.
5. Morgante et al.Comparison of two malignancy risk indices based on serum CA125, ultrasound score and menopausal status in the diagnosis of ovarian masses. BJOG: An International Journal of Obstetrics & Gynaecology 1999;106(6):524-527.
6. Leelahakorn S, Tangjitgamol S, Manusirivithaya, et al. Comparison of ultrasound score, CA125, menopausal status, and risk of malignancy index in differentiating between benign and borderline or malignant ovarian tumors. J Med Assoc Thai2005; 88:22-30.
7. Benjapibal M, Neungton C. Pre-operative prediction of serum CA 125 level in women with ovarian masses. J Med Assoc Thai. 2007;90:1986-91.
8. Jacobs I, Oram D, Fairbanks J, et al. A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate pre-operative diagnosis of ovarian cancer. Br J Obstet Gynaecol, 1990;97:922-9.

9. Tingulstad S, Hagen B, Skjeldestad FE, et al. Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the preoperative diagnosis of pelvic masses. Br J Obstet Gynaecol, 1996;103:826-31.
10. K. Uma Devi. Current status of gynaecological cancer care in India. J Gynecol Oncol 2009;20(2):77-80.
11. Young RH. A brief history of the pathology of gonads – A review. Mod Pathol 2005; 18: 3-17.
12. David J, Ashely B. Evans histopathological appearance of tumors. 4th Ed. New York: Churchill Livingstone Pvt. Ltd; 1990.
13. Parker D, Bradely C, Bogle SM. Serum albumin and CA-125 are powerful predictors of survival in epithelial ovarian cancer Br J Obset Gynecol 1994; 101: 888-93.
14. Hellstrom I, Raycraft J, Hayden Led Better M, Led Better JA, Schummer M, Mc Inthosh M et al. The HE4 (WFDC2) Protein is a biomarker for ovarian carcinoma. Cancer Research 2003; 63(13): 3695-700.
15. Jemal A, Murray T, Ward E, et al (2005). Cancer statistics, 2005. CA: A Cancer Journal for Clinicians, 55, 10–30.
16. Sharma JB, Gulati N. Gynecological disorders in geriatric age group. J Obstet Gynecol India 1990; 40: 459-63.
17. Maheshwari V. Surface epithelial tumors of ovary. Ind J Pathol Microbiol 1994; 37: 75-85.
18. Ramachandran G, Hiralal K, Chinnamma K, Thangavelu. Ovarian neoplasms - A study of 909 cases. J Obstet Gynaec India 1972; 22 309- 12.

19. Sikar K, Kumar P, Roy Chowdary NN. A study of ovarian malignancy – A review of 149 cases. J Obstet Gynaec India 1981; 31: 478-81.
20. Serov SF, Scully RE, Sabin LH. International Histological classification of tumor. No. 9, Histological typing of ovarian tumors. Geneva: World Heath Organisation; 1973.
21. Fox H, Wells M. Haines and Taylor obstetrical and gynecological pathology. Vol 1. 5th Edition, London: Churchill Livingstone Pvt. Ltd; 2003.
22. Gupta SC, Singh PA, Mehrotra TN, Agarwal R. A clinicopathological study of ovarian tumors. Indian J Pathol Microbiol 1986; 29: 354-62.
23. Maheshwari V. Surface epithelial tumors of ovary. Ind J Pathol Microbiol 1994; 37: 75-85.
24. Aure JC, Hoegk S, Kolsad H. Clinical and histological studies of ovarian carcinoma - A long term follow up of 990 cases. Am J Obstet Gynecol 1973; 37: 109-13.
25. Sampson JA. The endometroid carcinoma of the ovary. Arch Surg 1920; 1: 10-15.
26. Roth LM, Ovarian Brenner tumors, metaplastic, proliferating and low malignant potential. Cancer 1985; 56: 582-91.
27. Calondex C, Loffler J. Tumors of the female genital tract. In diagnostic histopathology of tumors. Vol 1, 2nd Edition, Philadelphia: Churchill Livingstone Pvt. Ltd; 2000.
28. Young RH, Scully RE. Ovarian sex cord stromal tumors - Recent progress. Int J Gynecol Pathol 1982; 1: 101-23.
29. Evans AT, Gaffey TA. Clinicopathologic review of 118 granulosa and 82 theca cell tumor. Obstet and Gynecol 1980; 55: 231-8.

30. Young RH, Scully RE. Ovarian Sertoli-leydig cell tumor. Int J Gynecol Pathol 1984; 2: 349-63.
31. Saxena H, Gupta S. Malignancies of the ovary. J Obset Gynecol India 1978; 28: 271-8.
32. Chenot J. Dysgerminoma. J Obstet Gynecol Br Emp 1950; 19: 507-511.
33. Gerbie MV. Primary choriocarcinoma of the ovary. Obstet Gynecol 1975; 46: 720-8.
34. Kumar V, Abbas AK, Fausto N, Robbins, Cortan. Pathologic basis of disease. 17th Edition, Philadelphia: Elsevier Pvt. Ltd. 2004.
35. Bast RC, Klug TL, St. John E, Jenison E, Niloff JM, Lazarus H et al. A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. N Engl J Med 1983; 309: 883-7.
36. Herbst AL. The epidemiology of ovarian carcinoma and the current status of tumor markers to detect disease (Review). Am J Obstet Gynecol 1994; 170: 107-9.
37. Woolas RP, Xu FJ, Jacobs IJ, Yu YH, Daly L, Berchuck A et al. Elevation of multiple serum markers in patients with stage I ovarian cancer. J Nat Cancer Inst 1993; 85: 1748-51.
38. Jacobs I, Davies AP, Bridges J, Stabile I, Fay T, Reynolds C et al. Multimodal approach to screening for ovarian cancer. Lancet 1988; 1: 268-71.
39. Sheiko MC, Hart RW. Dysgerminoma and elevated serum lactic dehydrogenase – A case report and Review. Cancer 1982; 49: 994-8.
40. Chervanak FA, Issacson GC, Campbell S. Gynaecological Malignancy. In: Morley P, Hollman AS (eds). Ultrasound in Obstetrics and Gynaecology. 1st Ed. 1993, 1746-59.

41. Sanders RC, Jammes AE. The Principles and Practice of Ultrasonography in Obstetrics and Gynaecology. 3rd Ed. 1985 Appleton- Century Crofts, 473-516.
42. Lawson TL, Albarelli JN. Diagnosis of gynaecologic pelvic masses by gray scale ultrasonography. Analysis of specificity and accuracy. Amer J Radiol 1977; 128: 1003-6.
43. Callen PW. Ovarian Sonography. In: Dillmacky MJ, Atri M (eds). Ultrasonography in Obstetrics and Gynaecology. 4th Ed. 2000 W B Saunders Company, 857-90.
44. Kurjak A. Adnexal Tumours. In: Kurjak A, Jalud I (eds). An Atlas of Ultrasonography in Obstetrics and Gynaecology. 1st Ed. 1995 CBS Publishers, 171-85.
45. Outwater EK, Siegelman ES, Hunt JL. Ovarian teratomas: tumor types and imaging characteristics. Radiographics 2001;21:475-490.
46. Sisler CL, Siegel MJ. Ovarian teratomas: a comparison of the sonographic appearance in prepubertal and postpubertal girls. AJR Am J Roentgenol 1990;154:139-141.
47. Quinn SF, Erickson S, Black WC. Cystic ovarian teratomas: the sonographic appearance of the dermoid plug. Radiology 1985;155: 477–478.
48. Patel MD, Feldstein VA, Lipson SD, Chen DC, Filly RA. Cystic teratomas of the ovary: diagnostic value of sonogra- phy. AJR Am J Roentgenol 1998;171: 1061–1065.
49. Sheth S, Fishman EK, BuckJL, Hamper UM, Sanders RC. The variable sonographic appearances of ovarian terato- mas: correlation with CT. AJR 1988;151:331-334.

50. Patel MD, Feldstein VA, Lipson SD, Chen DC, Filly RA. Cystic teratomas of the ovary: diagnostic value of sonogra- phy. AJR Am J Roentgenol 1998;171: 1061–1065.
51. JacobsI,OramD,FairbanksJ,TurnerJ,FrostC,Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preopera- tive diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990;97:922–9.
52. Mol BW, Boll D, De Kanter M, Heintz AP, Sijmons EA, Oei SG, et al. Distinguishing the benign and malignant adnexal mass: an external validation of prognostic models. Gynecol Oncol 2001;80:162–7.
53. Daponte A, Stergioti E, Messinis IE. Risk scoring for adnexal masses and endoscopic management. Int J Gynaecol Obstet 2007;96:42–3.
54. Aslam N, Tailor A, Lawton F, Carr J, Savvas M, Jurkovic D. Prospective evaluation of three different models for the pre-operative diagnosis of ovarian cancer. BJOG 2000;107: 1347–53.
55. Van Calster B, Timmerman D, Lu C, Suykens JA, Valentin L, Van Holsbeke C, et al. Preoperative diagnosis of ovarian tumors using Bayesian kernel-based methods. Ultrasound Obstet Gynecol 2007;29:496–504.
56. Lijmer JG, Mol BW, Heisterkamp S, Bonsel GJ, Prins MH, van der Meulen JH, et al. Empirical evidence of design- related bias in studies of diagnostic tests [published erratum appears in JAMA 2000;283:1963]. JAMA 1999;282:1061–6.
57. Van Houwelingen HC, Zwinderman KH, Stijnen T. A biva- riate approach to meta-analysis. Stat Med 1993;12:2273–84.

58. Van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta- regression. Stat Med 2002;21:589–624.
59. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and speci- ficity produces informative summary measures in diagnostic reviews. J Clin Epidemiol 2005;58:982–90.
60. Morgante G, la Marca A, Ditto A, De Leo, V. Comparison of two malignancy risk indices based on serum CA 125, ultra- sound score and menopausal status in the diagnosis of ovarian masses. Br J Obstet Gynaecol 1999;106:524–7.
61. Andersen ES, Knudsen A, Rix P, Johansen B. Risk of malignancy index in the preoperative evaluation of patients with adnexal masses. Gynecol Oncol 2003;90:109–12.
62. Ma S, Shen K, Lang J. A risk of malignancy index in preoperative diagnosis of ovarian cancer. Chin Med J (Engl) 2003;116:396–9.
63. Valentin L, Hagen B, Tingulstad S, Eik-Nes S. Comparison of 'pattern recognition' and logistic regression models for dis- crimination between benign and malignant pelvic masses: a prospective cross validation. Ultrasound Obstet Gynecol 2001;18:357–65.
64. Torres JC et al. Risk-of-malignancy index in preoperative evaluation of clinically restricted ovarian cancer. Sao Paulo Med J. 2002 May 2; 120(3):72-76.
65. Shuiqing MA et al. A risk of malignancy index in preoperative diagnosis of ovarian cancer. Chinese Medical Journal2003;116(3):396-399.

66. JacobsI, OramD,FairbanksJ,TurnerJ,FrostC,Grudzinskas JG. A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preopera- tive diagnosis of ovarian cancer. Br J Obstet Gynaecol 1990; 97:922–9.
67. Tahereh Ashrafgangooei, Mahdieh Rezaeezadeh. Risk of Malignancy Index in Preoperative Evaluation of Pelvic Masses Asian Pacific J Cancer Prev 2011;12:1727-1730.
68. Fanny Hakasson et al. Risk of malignancy index used as a diagnostic tool in a tertiary centre for patients with a pelvic mass. Acta Obstetricia et Gynecologica Scandinavica 2012;91(4):496-502
69. E Ferrazi et al Transvaginal ultrasonographic characterization of ovarian masses:Comparison of five scoring systems in a multicenter study ultrasound obstet.Gynecol.10(1997) 192-197
70. Yamamoto Y, Yamada R, Oguri H, Maeda N, Fukaya T. Comparison of four malignancy risk indices in the preope- rative evaluation of patients with pelvic mass. European journal of obstetrics, gynecology, and reproductive biology 2009; 144(2): 163-7
71. Manjunath AP, Pratapkumar, Sujatha K, Vani R. Compari- son of three risk of malignancy indices in evaluation of pelvic mass. Gynecologic oncology 2001 May; 81(2): 225- 9
72. Clarke SE, Grimshaw R, Rittenberg P, Kieser K, Bentley J. Risk of malignancy index in the evaluation of patients with adnexal masses. J Obstet Gynaecol Can. 2009;31:440–445.

ANNEXURE-II
DATA COLLECTION INSTRUMENT

TITLE: EFFECTIVENESS OF RISK OF MALIGNANCY INDEX TO DIFFERENTIATE BENIGN FROM MALIGNANT OVARIAN MASSES

Serial Number ☐☐ Date ☐☐☐☐☐☐☐☐

OPD No. ☐☐☐☐☐☐☐ IP No. ☐☐☐☐☐☐☐

Patients Name _____

Age: ☐☐ years

Address: _____

Contact No. _____

Parity a. Nulli gravida b. Nulli para ☐

c. Primi para d. Multi para

History of previous pelvic surgery

a. Yes b. No ☐

Symptoms

Pain in abdomen a. Yes b. No ☐

Mass per abdomen a. Yes b. No ☐

Risk of malignancy index scores

Menopausal status a. Pre menopausal (1) b. Post menopausal (3) ☐

CA 125 ☐☐☐☐

Variables to be measured in scan TVS/TAS: (Tick the variables which applied out of the 4 major variables)

Inner wall structure

Smooth or irregularities < 3 mm	(0)
……	(1)
Solid or non applicable	(2)
Pappilarities > 3 mm	(3)

Shadowing

Yes	(0)
No	(1)

Septa

No septa or thin < 3 mm	(0)
Thick > 3 mm	(1)

Echogenicity

Sonulucent/Low level echo or echogenic core	(0)
…….	(1)
…….	(2)
Mixed or high	(3)

Total score ☐

USG score for RMI ☐

RMI index

Menopausal status x USG score x CA 125

☐☐☐☐

Histopathological report

Serial Number	In/Out Patient Number	Age (Years)	History			Symptoms		Investigations												Side	Type of lesion
									Ultrasound score												
			Parity	Menopausal status	Pelvic surgery	Pain abdomen	Mass per abdomen	CA 125	Inner wall structures	Shadowing	Septa	Ethogenicity	Total score	RMI Score for USG	RMI Score	Lesions based on RMI Score	Histopathological report			
1	447041	45	m	3	+	+	+	81.00	0	1	1	1	3	3	729	M	Ovarian adenocarcinoma	L	M
2	446950	35	m	1	+	+	-	64.50	0	1	1	0	2	3	194	B	Mucinous cystadenoma	R	B
3	450167	55	m	3	-	+	+	10.00	0	1	1	0	2	3	90	B	Ovarian dermoid cyst	R	B
4	448952	48	m	1	-	+	+	7.20	0	1	0	1	2	3	22	B	Ovarian dermoid cyst	R	B
5	451621	48	m	3	+	+	-	96.10	0	1	0	0	1	1	288	M	Ovarian haemorrhagic cyst	R	B
6	451621	48	m	3	+	+	-	96.10	0	1	0	1	2	3	865	M	Ovarian serous adenocarcinoma	L	M
7	452129	20	p	1	-	+	+	1.70	0	1	0	0	1	1	2	B	Ovarian cystadenofibroma	R	B
8	448891	20	p	1	-	+	+	2.10	0	1	0	0	1	1	2	B	Serous cystadenoma	L	B
9	460338	45	m	1	-	+	+	230.00	2	1	0	3	6	3	690	M	Mass of unknown origin	-	B
10	459597	30	p	1	-	+	-	78.00	2	1	0	3	6	3	234	M	Ovarian haemorrhagic cyst	L	B
11	459677	70	m	3	+	+	+	13.70	0	1	1	0	2	3	123	B	Mixed serous and mucinous cystadenoma	R	B
12	488789	51	m	1	-	+	+	5.20	0	1	1	3	5	3	16	B	Mucinous cystadenoma	-	B
13	497256	45	m	3	-	+	-	9.10	0	1	0	0	1	1	27	B	Serous cyst	R	B
14	469747	72	m	3	-	+	-	10.00	0	1	1	0	2	3	90	B	Ovarian serous cyst	L	B
15	474580	35	m	1	-	+	-	23.30	3	1	0	3	7	3	70	B	Ovarian serous cyst	R	B
16	473752	28	p	1	-	+	-	9.80	0	1	0	0	1	1	10	B	Ovarian serous cyst	R	B
17	475898	27	m	1	-	+	+	7.30	0	1	0	0	1	1	7	B	Ovarian haemorrhagic cyst	R	B
18	2092798	30	m	1	-	+	-	6.20	3	1	0	3	7	3	19	B	Not operated	R	-
19	2092798	30	m	1	-	+	-	6.20	3	1	0	3	7	3	19	B	Not operated	L	-
20	479151	41	m	1	-	+	-	4.40	0	1	0	0	1	1	4	B	Ovarian simple cyst	R	B

21	2143844	19	p	1	-	-	-	4.10	0	1	0	0	1	**1**	4	**B**	Not operated	-	-
22	485119	68	m	3	-	+	+	26.00	0	1	1	3	5	**3**	234	**M**	Not operated	-	-
23	494000	48	m	3	+	+	-	13.50	0	1	1	3	5	**3**	122	**B**	Serous cystadenoma		B
24	218342	56	m	1	-	-	-	20.00	0	1	1	0	2	**3**	60	**B**	Dermoid cyst	R	B
25	447451	70	m	3	-	+	+	65.00	3	1	1	2	7	**3**	585	**M**	Papillary adenocarcinoma	L	M
26	484371	70	m	3	-	+	+	65.00	3	1	1	3	8	**3**	585	**M**	Papillary adenocarcinoma	R	M
27	274484	51	m	3	-	+	+	55.00	3	1	1	0	5	**3**	495	**M**	Papillary adenocarcinoma		M
28	424122	50	m	3	+	+	+	89.00	2	1	0	3	6	**3**	801	**M**	Ovarian adenocarcinoma	R	M
29	483183	28	m	1	-	+	+	12.00	0	1	1	0	2	**3**	36	**B**	Ovarian mucinous cystadenoma	R	B
30	483867	16	p	1	-	+	+	7.20	0	1	0	0	1	**1**	7	**B**	Serous cystadenoma	R	B
31	490226	48	m	3	+	+	+	80.00	2	1	1	3	7	**3**	720	**M**	Mucinous cystadeno carcinoma	R	M
32	490226	48	m	3	+	+	+	80.00	2	1	1	3	7	**3**	720	**M**	Mucinous cystadeno carcinoma	L	M
33	492783	57	m	3	-	+	-	3916.00	0	1	1	0	2	**3**	35244	**M**	Tube adenocarcinoma	L	M
34	495547	20	p	1	-	+	-	9.50	0	1	1	0	2	**3**	29	**B**	Serous cystadenoma	R	B
35	495547	20	p	1	-	+	-	10.00	0	1	1	0	2	**3**	30	**B**	Serous cystadenoma	L	B
36	496006	25	m	1	-	+	-	57.50	0	1	0	3	4	**3**	173	**B**	Mucinous cystadenoma	R	B
37	497069	58	m	1	-	+	-	8.60	2	1	0	3	6	**3**	26	**B**	Granulosa cell tumor	R	B
38	500491	13	p	1	-	+	+	298.10	0	1	0	3	4	**3**	894	**M**	Ovarian dysgerminoma	R	M
39	487171	25	m	1				8.40	0	1	0	0	1	**1**	8	**B**	ovarian serouscystadenoma	L	B
40	228644	50	m	3	-	+	+	13.60	0	1	0	0	1	**1**	41	**B**	Serous cystadenoma	R	B
41	2311912	28	p	1	-	+	-	4.60	0	1	0	0	1	**1**	5	**B**	Not operated	-	-
42	2311243	27	m	1	-	+	-	3.40	0	1	0	0	1	**1**	3	**B**	Not operated	-	-
43	486795	30	m	1	-	+	-	5.80	0	1	0	0	1	**1**	6	**B**	Serous cyst	R	B
44	209976	27	p	1	-	+	-	9.20	0	1	0	0	1	**1**	9	**B**	Not operated	-	-
45	502610	15		1	-	+	+	8.90	0	1	0	0	1	**1**	9	**B**	Yolksac tumor	L	M
46	521099	50	m	3	+	+	-	8.10	0	1	0	0	1	**1**	24	**B**	Serous cystadenoma	R	B
47	539983	35	m	1	-	+	-	23.30	0	1	1	0	2	**3**	70	**B**	Papillary serous cystadenoma	L	B
48	501143	70	m	3	-	+	+	7.50	0	1	0	0	1	**1**	23	**B**	Mucinous cystadenoma	L	B
49	516863	34	m	1	-	+	-	6.50	0	1	0	1	2	**3**	20	**B**	Simple cyst	R	B
50	524087	30	m	1	+	+	+	8.00	0	1	0	0	1	**1**	8	**B**	Dermoid cyst	R	B
51	506678	14	-	1	-	+	-	11.60	0	1	0	0	1	**1**	12	**B**	Serous cystadenoma	L	B

52	506678	28	p	1	-	+	-	11.60	0	1	0	0	1	**1**	12	**B**	Serous cystadenoma	R	B
53	509956	50	m	3	+	+	-	22.50	3	1	0	3	7	**3**	203	**M**	Brenner tumor	-	M
54	515947	28	p	1	-	+	-	6.00	0	1	0	1	2	**3**	18	**B**	Mucinous cystadenoma	L	B
55	521099	23	-	1	-	+	-	6.20	0	1	0	0	1	**1**	6	**B**	Serous cystadenoma	R	B
56	519950	40	m	3				31.00	3	1	1	3	8	**3**	279	**M**	MESENTERIC TUMOUR		B
57	526448	28	m	1	-	+	-	31.20	0	1	0	3	4	**3**	94	**B**	Mucinous cystadenoma	R	B
58	526448	28	m	1	-	+	-	31.20	0	1	0	0	1	**1**	31	**B**	Mucinous cystadenoma	L	B
59	526381	25	m	1	-	+	-	8.00	0	1	0	3	4	**3**	24	**B**	Serous cystadenoma	R	B
60	526585	70	m	3	+	+	+	2968.30	2	1	0	0	3	**3**	26715	**M**	Not operated	-	-
61	526859	14	-	1	-	+	+	4.10	0	1	1	0	2	**3**	12	**B**	Serous cyst	R	B
62	526859	14	-	1	-	+	+	4.10	0	1	1	0	2	**3**	12	**B**	Serous cyst	L	B
63	434382	32	m	3	-	+		34.00	2	1	0	3	6	**3**	306	**M**	Mucinous cystadenoma	R	B
64	516086	25	m	1				10.00	0	1	0	0	1	**1**	10	**B**	Serous cyst	R	B
65	528304	53	m	3	+	-	+	10.00	0	1	0	0	1	**1**	30	**B**	not operated	-	-
66	528304	53	m	3	+	-	+	10.00	0	1	0	1	2	**3**	90	**B**	not operated	-	-
67	533379	47	m	1	-	+	+	66.90	3	1	1	0	5	**3**	201	**M**	Ovarian papilary serous tumor	L	M
68	533379	47	m	1	-	+	+	66.90	0	1	0	1	2	**3**	201	**M**	Serous cystadenoma	R	B
69	536631	45	m	1	-	+	+	13.40	3	1	1	3	8	**3**	40	**B**	Mucinous cystadenoma	L	B
70	536632	28	m	1	-	+	+	8.80	0	1	1	3	5	**3**	26	**B**	Mucinous cystadenoma	R	B
71	537073	32	m	1	-	+	-	13.10	0	1	0	0	1	**1**	13	**B**	Simple cyst	L	B
72	537713	50	-	3	-	+	+	2060.00	0	1	1	3	5	**3**	18540	**M**	Serous papillary adenocarcinoma	L	M
73	537713	50	-	3	-	+	+	2060.00	0	1	1	3	5	**3**	18540	**M**	Serous papillary adenocarcinoma	R	M
74	524258	30	m	1	-	+	-	5.4	0	1	0	0	1	**1**	5.4	**B**	Mucinous cystadenoma	R	B

ANNEXURE-III

KEY TO MASTER CHART:

M: Malignant

B: Benign

p: Primigravida

m: Multigravida

L: Left side

R: Right side

(+): Present

(−): Absent

ANNEXURE-I
INFORMED CONSENT FORM FOR PARTICIPATION IN THE RESEARCH STUDY

TITLE: Effectiveness of Risk of malignancy index (RMI) to differentiate benign from malignant ovarian masses – A cross sectional study.

Objective/ Purpose of the study: We request you to participate in a study conducted by Dr.Snehal Shintre, Mobile no: 7353166104,Postgraduate in the Department of Obstetrics and Gynaecology KLE University's Teaching Hospital, Belgaum, under the direct supervision and guidance of Dr. M. C. Metgud $_{MD,FICOG}$ Professor, Department of Obstetrics and Gynaecology, KLE University's Teaching Hospital, Mobile no; 9448527667.The study is an attempt to study the effectiveness of Risk of malignancy index (RMI) to differentiating benign from malignant ovarian masses. Patient who fulfill the eligibility criteria will be included in the study. Your participation in the study will help us to derive a conclusion, which will be beneficial to the larger population.

Procedures: You will be asked to provide some personal identification information and gyanecological history relevant to the study. You will be subjected to investigations for CA125, USG and histopathological reports.

Risk and Benefits: There are no additional risks involved in the procedure. There will be no financial incentives for being a part of the study.

Your participation in the study is purely voluntary. Your decision will not affect your relationship with the institute or in the standard of care provided to you.

You are free to withdraw at any time during study.

Privacy and confidentiality: Every effort will be made to protect the confidentiality of the information provided by you. Results of the study may be published for scientific purposes, but your name will not be used.

If you have any questions about the study, you can contact Dr M. C. Metgud $_{MD,FICOG.}$, Professor Department of Obstetrics and Gynaecology. In case you need any further information regarding your rights as a study participant, you may please contact Dr. V. D. Patil, Principal and Dr. P. V. Patil, Chairman of JNMC, Institute Ethics Committee, Mobile no: 9448190231.

I volunteer and consent to participate in the study. I have read the consent or have read to me. The study has been fully explained to me and I was given an opportunity to ask questions and receive answers.

Signature/thumb impression of participant:

Signature/thumb impression of witness:

Signature of the investigator:

Date:

संशोधन अभ्यासक्रमात भाग घेणाऱ्यांचे सम्मती जवाब

शिर्षक : अंडाशय संबंधी उदारतेचा परीणाम जबाबदारी सूचिका (आर्.एम्.आय्) गट ए घाटी विभागाचे अभ्यास

अभ्यास क्रमाचा उद्देश : डॉ. स्नेहल शिंत्रे, मो. नं. ७३५३१६६१०४ पोस्ट ग्रॅज्युयेट अब्सेट्रीक्स गॅनाकालॉजी डिपार्टमेंट के.एल्.ई विश्वविद्यालाय टीचींग हस्पताल बेळगांव यानीं डॉ. एम्. सी. मेटगुड् प्रोफेसर अब्सेट्रीक्स व गॅनाकालाजी डिपार्टमेंट के.एल्.ई विश्वविद्यालय टीचींग हस्पताल मो. नं. ९४४८५२७६६७ यांच्या सुपाविजन् खाली हाती घेतलेल्या अभ्यास क्रमात भाग घेणेस आपल्याला विनंती केले आहे. हा अंडाशय उदारतेचा परीणाम जबाबदारी (आर्.एम्.आय्) इंडेक्स पाहीले आहे. हे पेशंट गटात कोण यास योग्य आहे त्यानी ह्या अभ्यास क्रमात समावेश होणे. तुमचा समावेश बरेच लोकानां सहाय्यक होईल, कारण त्याच्या वर आम्ही अभ्यास करून त्याचा लाभ बरेच लोकानां मिळेल.

पद्धत : आम्ही तुम्हास तुमच्या वैयक्तीक ओळख माहीती व बाळंतपणा बद्दल इतीहास सदर अभ्यासासाठी कळविणे आवश्यक आहे. आपणास सी.ए. १२५ युएस्.जी हिस्टोपॅथालाजीकल् वर्दी बाबत तपास करण्यात येईल.

जबाबदारी व लाभ : यात अतीरीक्त जबाबदारी नाहीं. व आर्थीक जबाबदारीही नाहीं. आपण भाग घेणेस स्वतंत्र राहील आपला निर्णय संस्था संबंधी परीणाम होणार नाहीं. किंवा आपणास मिळणारे उपचारात कोणतेही फेरबदल होणार नाहीं. अभ्यासा वेळी आपण पाहीचे तेव्हां यातून बाहेर जाऊ शकता.

खासगी व गोप्यता : आपण दिलेली माहीती व प्रत्येक परीणाम राखून गौप्यता राखण्याचे आहे. अभ्यासाचे परीणाम विज्ञान समजणूकी साठी जाहीर करण्यात येईल परंतु तुमचे नाव जाहीर करणार नाहीं.

ह्या अभ्यास क्रमात तुम्हास काहीं प्रश्न विचारणेचे असल्यास डॉ. मेटगुड् यानां संपर्क साधणे. आपण यात भाग घेतल्या हक्का बद्दल अतीरीक्त मेहीती पाहीजे असल्यास आपण डॉ. व्हि. डी पाटील प्रीन्सीपाल किंवा डॉ. पी. व्हि. पाटील चेअरमन् जे.एन्.एम्.सी. एथीक्स कमीटी मो. नं. ९४४८१९०२३१ यानां संपर्क साधणे.

मी, स्व-ईच्छेने या अभ्यास क्रमात भाग घेतले आहे. मी, सम्मती पत्र वाचले आहे. किंवा वाचून सांगण्यात आले आहे. अभ्यास क्रमातील पूर्ण तपशील मला सांगण्यात आले आहे. व मला प्रश्न करणेस उत्तर घेणेस अवकाश दिला आहे.

भाग घेणाऱ्यांची सही / हा. डा. हा. ठ.

साक्षीचे सही / हा. डा. हा. ठ.

इनवेस्टीगेटरांची सही

ता :

ಸಂಶೋಧನಾ ಅಭ್ಯಾಸದಲ್ಲಿ ಭಾಗವಹಿಸಿದವರ ಸಮ್ಮತಿ ಹೇಳಿಕೆ

ಶಿರ್ಷಿಕೆ : ಅಂಡಾಶಯಕ್ಕೆ ಸಂಬಂಧಿಸಿದಂತೆ ಉದಾರತೆಯ ಪರಿಣಾಮ ಜವಾಬ್ದಾರಿ ಸೂಚಿಕೆ (ಆರ್.ಎಮ್.ಐ) ಗುಂಪು ಎ ಫಾಟಿ ವಿಭಾಗದ ಅಭ್ಯಾಸ

ಅಭ್ಯಾಸ ಕ್ರಮದ ಉದ್ದೇಶ : ಡಾ : ಸ್ನೇಹಲ ಶಿಂತ್ರೆ ಮೊ. ನಂ. 7353166104 ಪೋಸ್ಟಗ್ರಾ ್ಯಜ್ಯುಯೇಟ್ ಅಬ್ಸೆಟ್ರಿಕ್ಸ ವ ಗ್ಯಾನಾಕಾಲಜಿ ಡಿಪಾರ್ಟಮೆಂಟ ಕೆ.ಎಲ್.ಇ. ವಿಶ್ವವಿದ್ಯಾಲಯ ಟೀಚಿಂಗ ಆಸ್ಪತ್ರೆ ಬೆಳಗಾವಿ ಇವರು ಡಾ: ಎಮ್. ಸಿ. ಮೆಟಗುಡ್ ಪ್ರೊಫೆಸರ್ ಆಬ್ಸೆಟ್ರಿಕ್ಸ ವ ಗ್ಯಾನಾಕಾಲಾಜಿ ಡಿಪಾರ್ಟಮೆಂಟ ಕೆ.ಎಲ್.ಇ. ವಿಶ್ವವಿದ್ಯಾಲಯ ಟಿಚಿಂಗ ಆಸ್ಪತ್ರೆ ಮೊ. ನಂ. 9448527667 ಇವರ ನೇರ ಮೇಲ್ವಿಚಾರಣೆಯಲ್ಲಿ ಕೈಕೊಂಡ ಅಭ್ಯಾಸ ಕ್ರಮದಲ್ಲಿ ಭಾಗವಹಿಸಲು ತಮ್ಮನ್ನು ವಿನಂತಿಸಿಕೊಳ್ಳಲಾಗಿದೆ. ಇದು ಅಂಡಾಶಯದ ಉದಾರತೆಯ ಪರಿಣಾಮವಾಗಿ ಜವಾಬ್ದಾರಿ (ಆರ್.ಎಮ್.ಐ) ಪರಿವಿಡಿ ಹೊಂದಿರುತ್ತದೆ. ಇದು ಪೇಶಂಟುಗಳ ಗುಂಪಿನಲ್ಲಿ ಯಾರು ಇದುಕ್ಕೆ ಅರ್ಹರಿರುವರೋ ಹಾಗೂ ಎಲ್ಲ ಸರಿ ಇರುವವರು ಈ ಅಭ್ಯಾಸ ಕ್ರಮದಲ್ಲಿ ಕೂಡಿಕೊಳ್ಳುವರು. ನಿಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆಯು ಬಹಳೇ ಜನರಿಗೆ ಸಹಾಯಕವಾಗುವದು ಯಾಕೆಂದರೆ ಆದರ ಮೇಲೆ ನಾವು ಅಭ್ಯಸಿಸಿ ಆದರ ಲಾಭ ಬಹಳಷ್ಟು ಜನರಿಗೆ ದೊರಕುವದು.

ಪದ್ಧತಿ : ನೀವು ನಮಗೆ ನಿಮ್ಮ ವೈಯಕ್ತಿಕ ಗುರುತು ಮಾಹಿತಿ ಹಾಗೂ ಹೆರಿಗೆ ಬಗ್ಗೆ ಇತಿಹಾಸ ಸದರೀ ಅಭ್ಯಾಸಕ್ಕಾಗಿ ತಿಳಿಸಬೇಕಾಗುತ್ತದೆ ತಮ್ಮನ್ನು ಸಿಎ125 ಯುಎಸ್‌ಜಿ ಹಿಸ್ಟೋಪ್ಯಾಥಾಲಾಜಿಕಲ್ ವರದಿ ಕುರಿತು ತಪಾಸಿಸಲಾಗುವದು.

ಹೊಣೆಗಾರಿಕೆ ಹಾಗೂ ಲಾಭಗಳು : ಇದರಲ್ಲಿ ಹೆಚ್ಚಿನ ಹೊಣೆಗಾರಿಕೆ ಸೇರಿಲ್ಲ ಹಾಗೂ ಆರ್ಥಿಕವಾಗಿ ಯಾವ ಹೊಣೆಗಾರಿಕೆಯೂ ಇಲ್ಲ.

ತಮ್ಮ ಭಾಗವಹಿಸುವಿಕೆ ಪೂರ್ಣ ಸ್ವತಂತ್ರವಾದುದು ತಮ್ಮ ನಿರ್ಣಯ ಸಂಸ್ಥೆ ಸಂಬಂಧದ ಮೇಲೆ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ ಆಥವಾ ತಮಗೆ ದೊರೆಯತಕ್ಕ ಉಪಚಾರದಲ್ಲಿ ಯಾವ ವ್ಯತ್ಯಾಸಗಳಾಗಲಾರವು. ಅಭ್ಯಾಸದ ವೇಳೆ ನೀವು ಬೇಕಾದಾಗ ಇದರಿಂದ ಹಿಂದೆ ಸರಿಯಬಹುದು.

ಖಾಸಗಿ ಹಾಗೂ ಗೌಪ್ಯತೆ : ತಾವು ನೀಡಿದ ಮಾಹಿತಿ ಹಾಗೂ ಪ್ರತಿಯೊಂದು ಪರಿಣಾಮವನ್ನು ರಕ್ಷಿಸಿ ಗೌಪ್ಯತೆ ಕಾಯ್ದುಕೊಳ್ಳಲಾಗುವದು ಅಭ್ಯಾಸದ ಪರಿಣಾಮವನ್ನು ವಿಜ್ಞಾನದ ತಿಳುವಳಿಕೆಗಾಗಿ ಪ್ರಸಿದ್ಧಿಸಲಾಗುವದು ಆದರೆ ನಿಮ್ಮ ಹೆಸರನ್ನು ಪ್ರಸಿದ್ಧಿಸಲಾಗುವದಿಲ್ಲ.

ಈ ಅಭ್ಯಾಸ ಕ್ರಮದ ಬಗ್ಗೆ ನಿಮಗೆ ಏನಾದರೂ ಪ್ರಶ್ನೆಕೊಳ್ಳುವದಿದ್ದರೆ ಡಾ : ಮೆಟ್‌ಗುಡ್ ಇವರನ್ನು ಸಂಪರ್ಕಿಸಬೇಕು. ತಾವು ಇದರಲ್ಲಿ ಭಾಗವಹಿಸಿದ ಹಕ್ಕಿನ ಬಗ್ಗೆ ಹೆಚ್ಚಿನ ಮಾಹಿತಿ ಬೇಕಾದಲ್ಲಿ ತಾವು ಡಾ : ವ್ಹಿ. ಡಿ. ಪಾಟೀಲ ಪ್ರಿನ್ಸಿಪಾಲ್ ಆಥವಾ ಡಾ : ಪಿ. ವಿ. ಪಾಟೀಲ ಚೇರಮನ್ ಜೆ.ಎನ್.ಎಮ್.ಸಿ ಎಥಿಕ್ಸ ಕಮೀಟಿ ಮೋ. ನಂ. 9448190231 ಇವರನ್ನು ಸಂಪರ್ಕಿಸಿರಿ.

ನಾನು ಸ್ವ ಇಚ್ಛೆಯಿಂದ ಈ ಅಭ್ಯಾಸ ಕ್ರಮದಲ್ಲಿ ಭಾಗವಹಿಸಿದ್ದೇನೆ. ನಾನು ಸಮ್ಮತಿ ಪತ್ರ ಓದಿದ್ದೇನೆ ಆಥವಾ ಓದಿ ಹೇಳಲಾಗಿದೆ ಅಭ್ಯಾಸ ಕ್ರಮವನ್ನು ಪೂರ್ಣವಾಗಿ ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ. ಹಾಗೂ ನನಗೆ ಪ್ರಶ್ನೆಗಳನ್ನು ಕೇಳಲು ಉತ್ತರ ಪಡೆಯಲು ಅವಕಾಶ ನೀಡಲಾಗಿದೆ.

ಭಾಗವಹಿಸಿದವರ ಸಹಿ/- ಈ. ಎ. ಹೆ. ಗು.

ಸಾಕ್ಷಿಯ ಸಹಿ/- / ಈ. ಎ. ಹೆ. ಗು