EARLY DETECTION OF OVARIAN CANCER

By
El-Barky, M.M.; El-Gendy, S.S.; El-Osh, S.S. and Nossiar, W.S.
Obstetrics and Gynecology Department
Faculty of Medicine, Zagazig University

ABSTRACT

Background: Ovarian cancer represent one of lethal malignancy if not discovered early. Most cases present in late stages, so early detection of cancer ovary is one of important item many researches try by different modalities for establishing the one or more methods for detection. **Objectives:** The aim of this work is to evaluate the risk factors of cancer ovary, determine the role of ultrasound ,CA_{125}, and Doppler for early detection of ovarian cancer and evaluate the efficacy of risk of malignancy index in detection of cancer ovary. **Patients and methods:** This study is performed for patients at Obstetrics and Gynecology Department (outpatient units, inpatient units and emergency units), Zagazig University Hospitals. It comprised 120 patients as a study group together with 10 apparently healthy females as a reference group. **Results:** We found the significance of CA125, ultrasound data (solid areas, papillae, length, depth, width), and risk of malignant index. By addition of Doppler data (PI& RI) the significance become more , and hence , by use statistical analysis we found new index by which the significance become more and more with sensitivity of 90.9%, specificity 88.4%, positive predictive value 93.3%, and negative predictive value 84.4%. There is significance from cigarette smoking, clomiphine citrae, FSH, and LH for cancer ovary development. **Conclusion:** Zagazig ovarian cancer equation has the most significance in early detection of cancer ovary.

INTRODUCTION

In 1968, the World Health Organization published disease screening guidelines which are still applicable today. In brief, the disease in question should represent a significant cause of mortality. Its natural course and treatment strategies should be well established. Early intervention should improve outcome. The screening tests should be readily available, accurate, cost-effective and well accepted by the population. Epithelial Ovarian Cancer (EOC) meets these criteria. In fact, it accounts for 4.0% of all cancer cases and 4.2% of all cancer deaths in women around the world **(1)**.

Treatment of the disease is well established and effective. Patients with early-stage disease have a much better prognosis with a significantly higher chance of cure. For ovarian cancer, however, over 60% of patients are diagnosed in advanced stages of the disease, which carry a high mortality. Thus, it is reasonable to speculate that tests that can detect ovarian cancer in its early stages will improve cure and thus reduce disease-related mortality **(2)**.

The aim of this work is to:

1- Evaluate the risk factors of cancer ovary.
2- Role of ultrasound, CA_{125}, and Doppler for early detection of ovarian cancer.
3- Evaluate the efficacy of risk of malignancy index in detection of cancer ovary.

PATIENTS AND METHODS

This was a Cross-sectional study performed for patients at Obstetrics and Gynecology Department (outpatient units, inpatient units and emergency units), Zagazig University Hospitals, between September 2007 and September 2010.

It comprised 120 patients as a study group together with 10 apparently healthy females as a reference group. The patient group was divided according to history into 2 main groups:

Group 1: It comprised 66 patients suspected of exposed risk of malignancy from history (e.g. positive family history, fertility medications, smoking, etc…).

Group 2: It comprised 54 patients suspected of no exposed risk of malignancy from history.

Inclusion criteria:

1- Any age.

2- Asymptomatic and symptomatic patients.
3- Coaperative patients.
4- Any adnexal cyst or mass.
5- Pregnancy with adenexal mass or cyst.
6- Positve family history of breast,colon,endometrial and ovarian cancers in group 1of study.
7- Any patient with previous surgery on ovaries with preserved ovarian tissue.

Exclusion criteria:

1- Pregnacy without mass or cyst.
2- Any case with acute pelvic infection.
3- Pateints with previos bilateral oophrectomy.

METHODS

All patients were subjected to the following:

1- History taking.
2- General examination including general look, vital signs, head-to-toe examination, chest and heart evaluation and abdominal examination.
3- Local examination including inspection, pelvic examination, bimanual examination and speculum examination.
4- 2-dimensional and 4-dimensional ultarsonography.
5- Doppler study of the mass.
6- Laboratory investigations including routine preoperative investigations e.g. complete blood count, liver function tests, kidney function tests and coagulation profile and specific investigations including CA_{125} using fully automated VIDAS® immunofluorescence assay.

VIDAS® CA_{125}II is an automated quantitative test for use on the VIDAS instruments, for the measurement of OC-125 antigenic determinants in human serum or plasma. The assay principle combines a 2-step enzyme immunoassay sandwich method with a final fluorescent detection.

7- Abdominal exploration (laparotomy or laparoscopy).
8- Pathological examination of mass.
9- Collecting information and data and subjecting these data to statistical analysis.

RESULTS

Table (1): Frequency of malignancy according to some variables

	Benign		Malignant		Total	X^2	p
	No	%	No	%			
Family history							
Absent	35	36.5	61	63.5	96	0.08	0.77
Present	8	33.3	16	66.7	24		
Examination							
Absent	10	50	10	50	20	2.09	0.14
Present	33	33	67	67	100		
Smoking							
Absent	25	35.7	45	64.3	70	0.001	0.97
Present	18	36	32	64	50		
Clomiphene							
Absent	39	38.2	63	61.8	102	1.706	0.191
Present	4	22.2	14	77.8	18		
FSH							
Normal	41	37.3	69	62.7	110	1.18	0.27
Absent	2	20	8	80	10		
LH							
Normal	41	38	62	62	108	2.13	0.14
Absent	2	16.7	10	83.3	12		

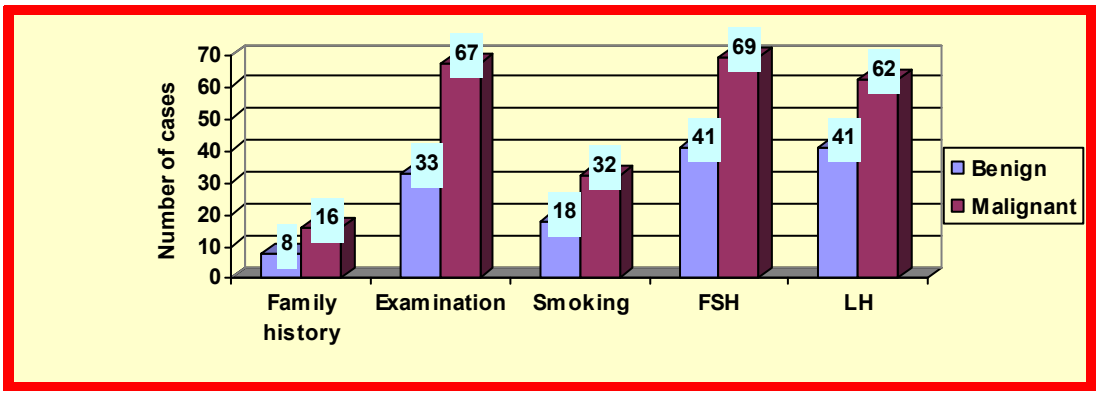

Figure (1): Frequency of malignancy according to some variables

Table (2):

	Benign		Malignant		TxPol	X^2	p
	No	%	No	%			
Cystic							
Absent	16	53.3	14	46.7		5.328	0.021
Present	27	30	63	70			
Solid							
Absent	10	100				19.535	0
Present	33	30	77	70			
Unilateral							
-ve	12	21.1	45	78.9		10.316	0.001
+ve	31	49.2	32	50.8			
Bilateral							
-ve	31	49.2	32	50.8		10.316	0.001
+ve	12	21.1	45	78.9			
Septa							
Absent	28	53.8	24	46.2		12.949	0
Present	15	22.1	53	77.9			
Internal papillae							
Absent	39	44.8	48	55.2		11.131	0.001
Present	4	12.1	29	87.9			
External papillae							
Absent	43	42.2	59	57.8		11.826	0.001
Present							

Table (3): Frequency of length, width, depth, PI, RI and CA_{125} among patients according to malignancy

	Benign (n = 43)	Malignant (n = 77)	t	p
Length	10.86 ± 3.6	12.9 ± 3.5	3.03	0.003
Width	9.65 ± 2.99	11.29 ± 3.5	2.05	0.01
Depth	8.55 ± 2.65	10.51 ± 3.1	3.45	0.001
PI	1.46 ± 0.81	0.52 ± 0.29	9.26	0
RI	0.51 ± 0.22	0.38 ± 0.16	3.36	0.001
CA_{125}				
Median	25	200	5.73[a]	0
Range	10-620	10-1900		

[a]Test used was Mann-Whitney-U test

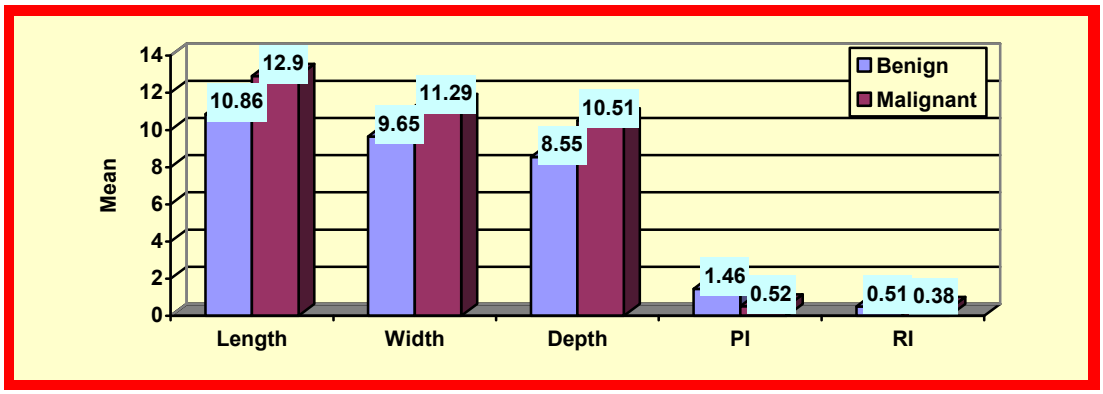

Figure (2): Frequency of length, width, depth, PI and RI among patients according to malignancy

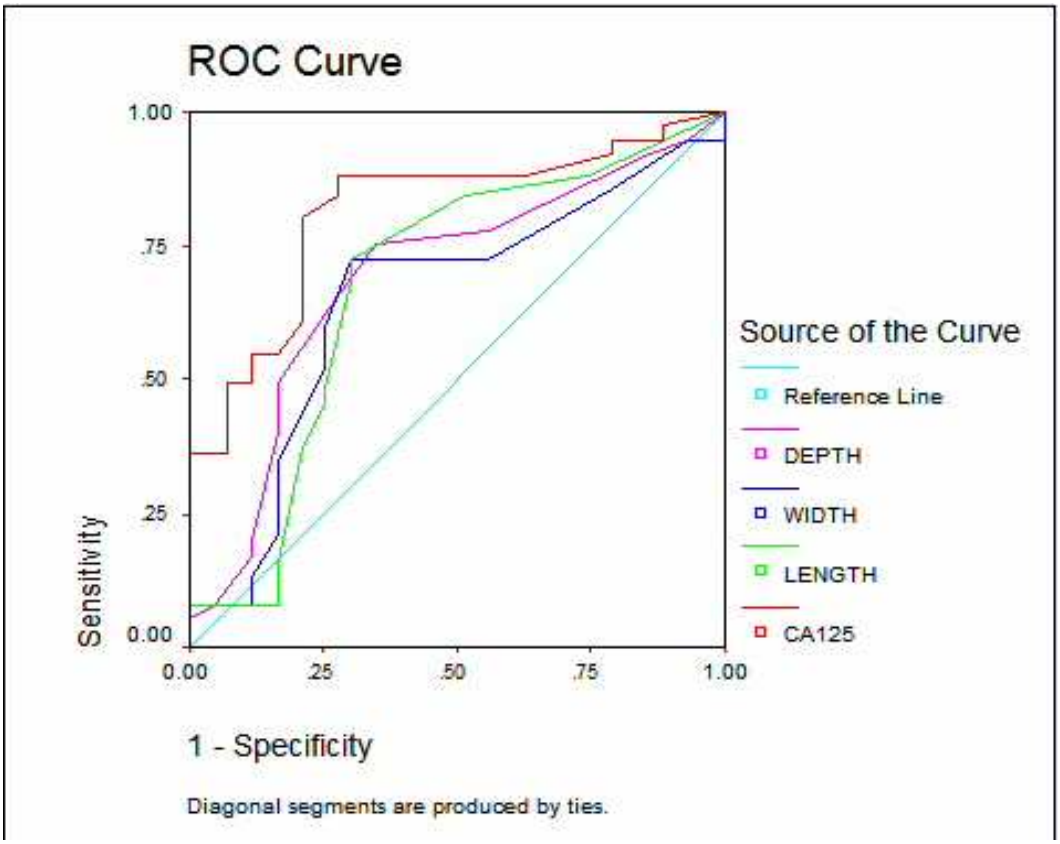

Figure (3): ROC curve of depth, width, length and CA-125

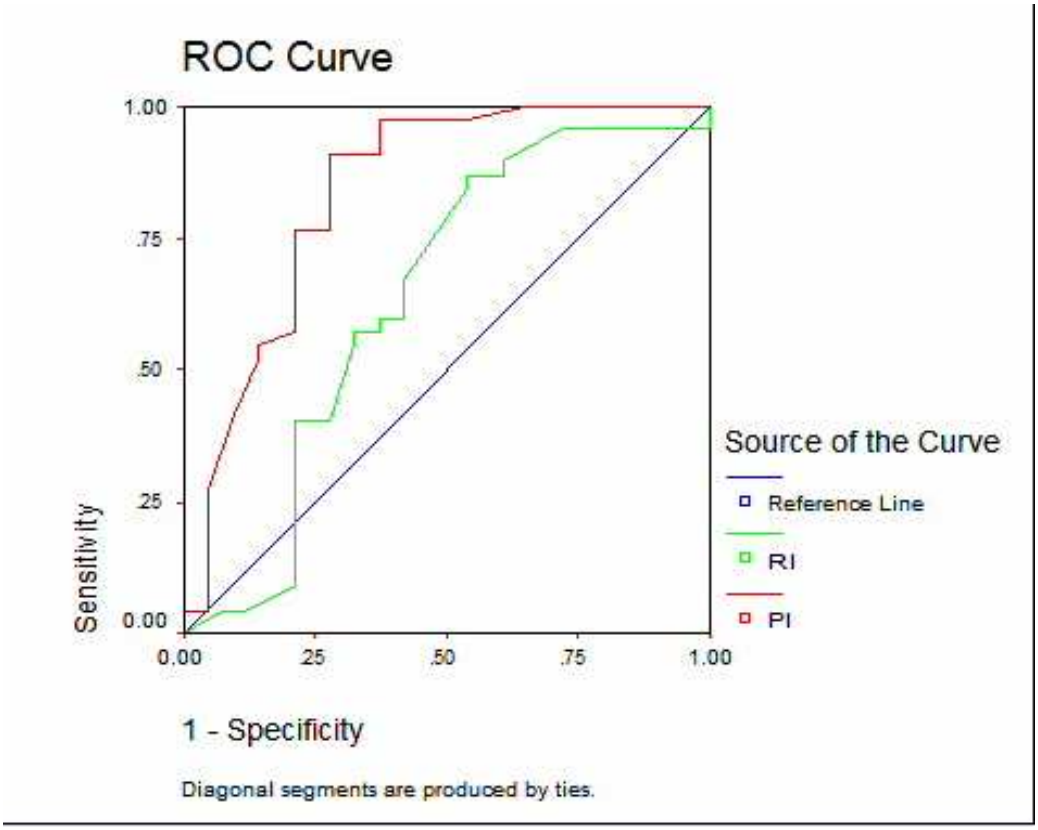

Figure (4): ROC curve of RI and PI

Table (4): Validity of CA_{125}, RMI, $PI_{0.86}$, RI and ZOCE in diagnosis of malignancy

	True +ve	True –ve	Sensitivity	Specificity	PPV	NPV	Kappa	p
CA_{125}	68	31	88.3%	72.1%	85%	77.5%	0.61	0
OCMI	65	19	84.4%	44.2%	73%	61.3%	0.3	0.001
$PI_{0.86}$	70	31	90.9%	72.1%	85.4%	81.6%	0.64	0
RI	65	20	84.4%	46.5%	73.9%	62.5%	0.32	0
ZOCE			90.9%	88.4%	93.3%	84.4%		

Table (5): Validity of CA-125 in diagnosis of malignancy

CA-125	Malignant	Benign	Total
> 35	68	12	80
< 35	9	31	40
Total	77	43	120

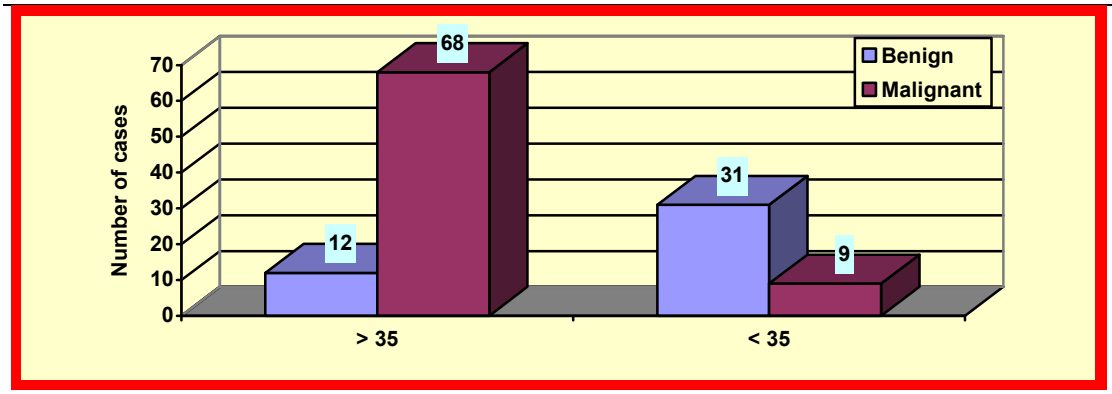

Figure (5): Validity of CA-125 in diagnosis of malignancy

Table (6): Frequency of malignancy

	No	%
Benign	43	35.84
Malignant	77	64.16

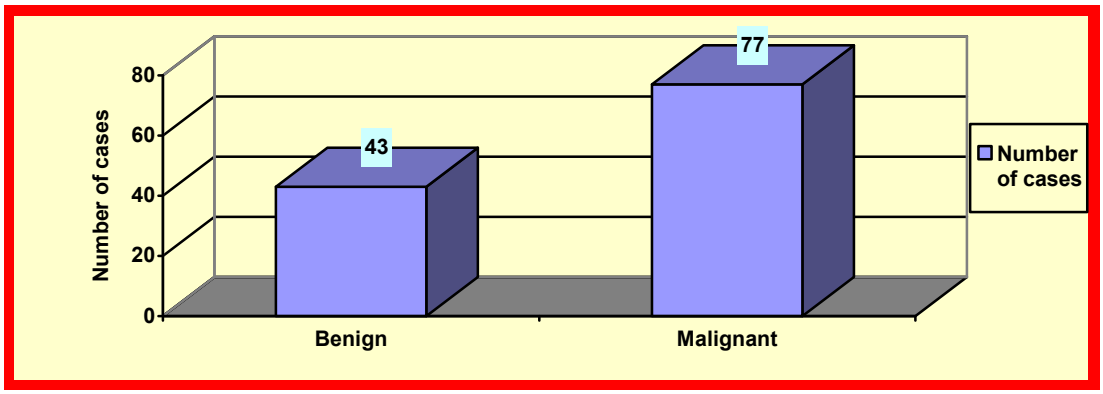

Figure (6): Frequency of malignancy

Table (7): Variables in the equation

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
CA125.35	3.475	.968	12.892	1	.000	32.295	4.845	215.250
PI.86	4.640	1.288	12.972	1	.000	103.593	8.291	1294.300
RI.51	.028	.925	.001	1	.976	1.028	.168	6.304
LENGH.R	-6.190	74.230	.007	1	.934	.002	.000	3.134631465256924E+60
WIDTH.R	15.368	104.975	.021	1	.884	4725052.238	.000	1.069442331470606E+96
DEPTH8.5	-7.139	74.236	.009	1	.923	.001	.000	1.228406810679774E+60
SOLID	9.677	121.372	.006	1	.936	15953.945	.000	3.272382374209535+107
BI	-1.395	.885	2.485	1	.115	.248	.044	1.404
INTE.PAP	3.864	1.761	4.813	1	.028	47.641	1.510	1503.314
EXT.PAP	21.558	128.574	.028	1	.867	2304590884.039	.000	6.376259165277210+118
Constant	-15.348	121.374	.016	1	.899	.000		

a Variable(s) entered on step 1: CA125.35, PI.86, RI.51, LENGH.R, WIDTH.R, DEPTH8.5, SOLID, BI, INTE.PAP, EXT.PAP.

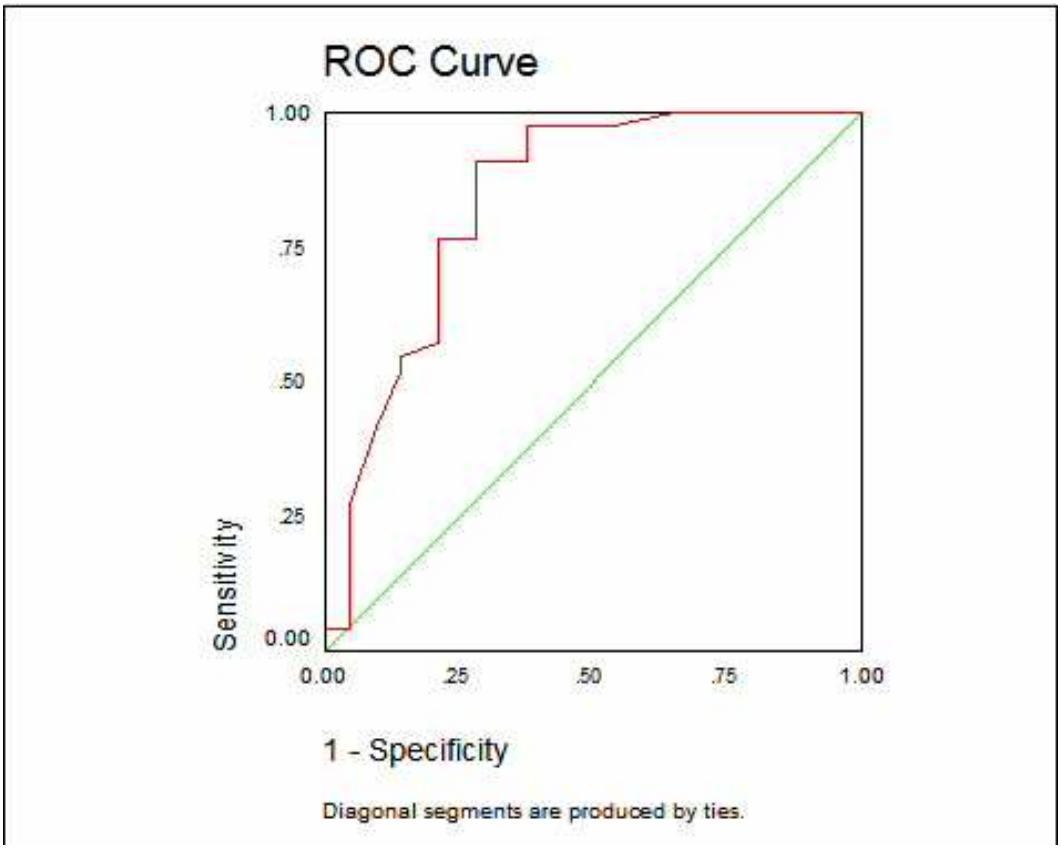

Figure (7)

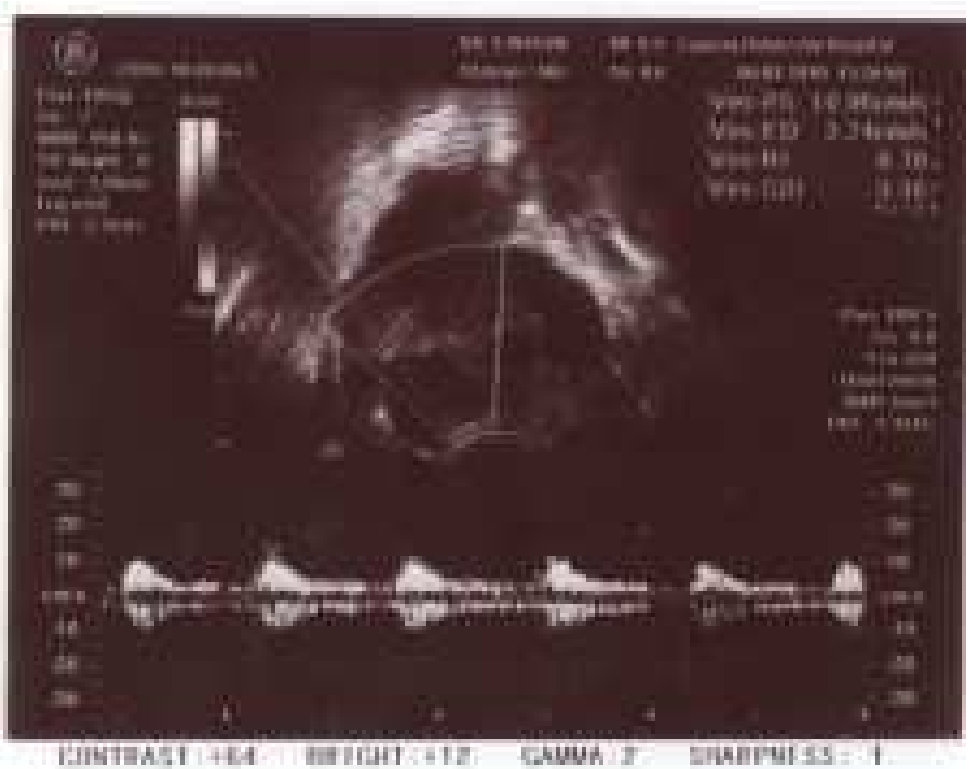

Figure (8): Doppler study of ovarian mass revealing neovascularization

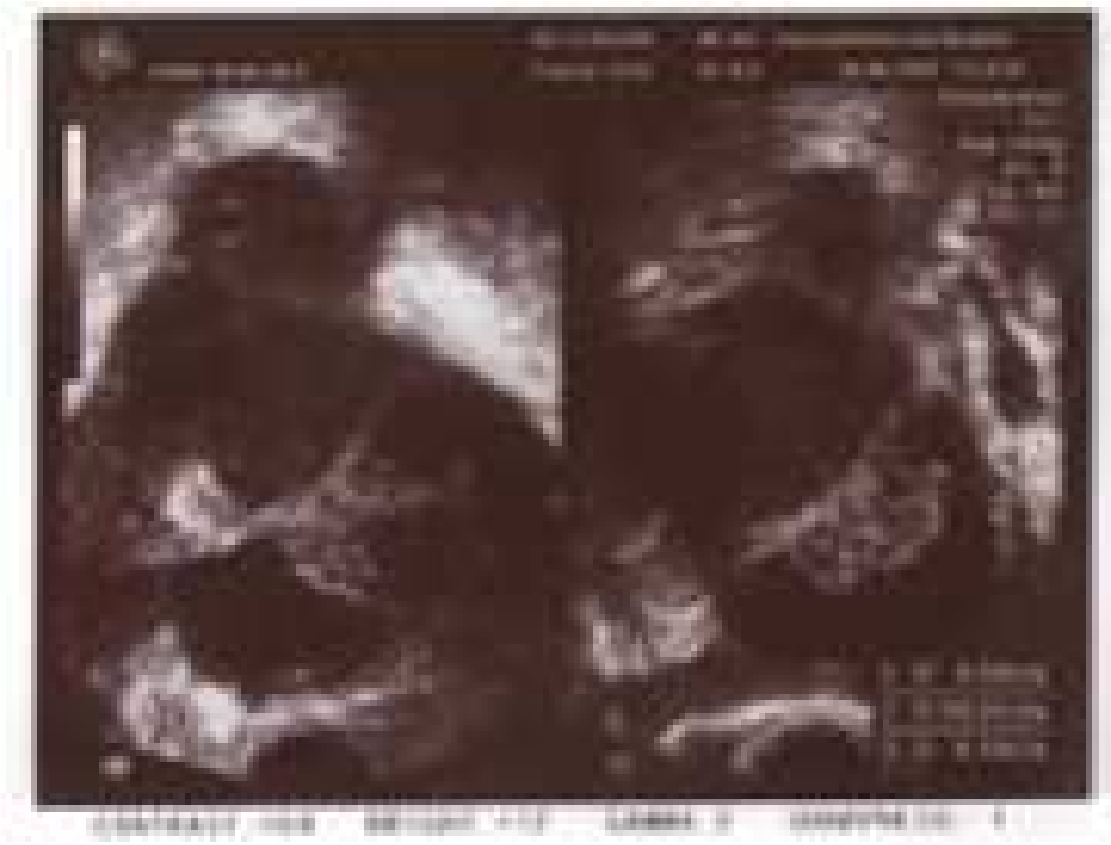

Figure (9): Ultrasound of adnexal mass revealing solid and cystic components

DISCUSSION

No ***age*** is immune against malignancy. There is wide range of difference in age of study and control groups. The range between 9 – 77 years. The age incidence in previous studies, age in cancer ovary more toward post menopause patients.

With positive ***family history of malignancy***, especially cancer ovary, breast, stomach and colon, cancer ovary is suspected. This more especially if proved by genetic analysis. But in this study no significant difference between positive and negative family history. This is due to genetic detesting and genetic family pedigree is not applicable , in addition to racial incidence is less than other countries.

Risk groups for sporadic ovarian cancer are defined by postmenopausal status and age (50) and for hereditary ovarian malignancy by family history criteria and presence of BRCAI and $BRCA_2$ mutations. The majority of ovarian cancers are sporadic and occur in the general population. Over 90% of sporadic cancers occur in women aged over 50, and screening studies in the general population usually target this group. A number of other factors affect risk in the general population including menopause, years of oral contraceptive use, and parity. Hereditary syndromes account for 5-10% of ovarian cancers. First-degree female relatives of affected members from ovarian or breast and ovarian or hereditary non-polyposis colon and ovarian cancer families have a lifetime risk of developing ovarian cancer of greater than 10%. Much of this risk is due to mutations arising in the $BRCA_1$ and $BRCA_2$ genes. The average cumulative risks by age 70 years for ovarian cancer is 39% (18-54%) in $BRCA_1$ mutation carriers and 11% (2.4-19%) in $BRCA_2$ mutation carriers **(3)**.

In women with strong evidence of a hereditary predisposition, screening from the age of 35 is frequently advocated although the efficacy of such surveillance is not yet established **(4)**.

Smoking is theoretically suspected to decrease the growth of germ cell and lead to premature ovarian failure. But carcinogenic effect of smoking in other tissues like lung ,cervix …etc , is more .the ovary is formed not only from germ cells but also from sex cord epithelium , fibrous stroma and epithelium deived from coelomic cavity has ability to differentiate to other tissue. the effect of smoking on non-germ cells of the ovary is not suspected, but in study there is increased incidence of mucinous cell tumor in smoker. in this study there is no significant deference between smoker and nonsmoker.

Baron et al. (5) study addressed the relationship between cigarette smoking and cancers of the breast , endometrium , uterine cervix, and ovary. The lifetime smoking history of cases was compared with that of controls, and relative risks (odds ratios) for smoking were estimated using multiple logistic regression to adjust for potential confounding by age, marital status, number of pregnancies, and Quetelet's index. With increasing amount smoked there was a statistically significant decrease in endometrial cancer risk and a statistically significant increase in cervical cancer risk. In the highest smoking category (greater than or equal to 15 pack-yr), the endometrial cancer relative risk was 0.57 [95% confidence interval (CI) of 0.37, 0.86] and the cervical cancer relative risk was 1.81 (95% CI of 1.47, 2.22). There was no apparent relationship between smoking and cancers of the breast or ovary.

Asymptomatic cases represent more than 40 % in most of studies. Cancer ovary mostly presents late in stage 3 or 4, sometimes discovered in early stages. Most common presentation is related to GIT upsets eg nausea, vomiting …..ect., in addition to abdominal pain and these manifestation represent about 75 % of manifestation of symptomatic cases and this the same as this study.

Abuse of ***FSH and LH*** for induction of ovulation , or hyperresponder patient may present the ovarian hyper stimulation syndrome with its hazards effect. Effect of FSH is either stimulation of growth of granulose cell and theca cells by growth factors or stimulation of oocyte which inturn stimulate granulose and theca cell by certain growth factor . are these mechanism of multiplications of cells can lead to ovarian cancer? But no detected significant difference between user of FSH and nonuser in this study or other.

Adam et al. (6) mentioned that There is concern about the long-term health impact of ovarian stimulation treatment for infertility, in particular the effect on cancer risk. The aim of his study was to investigate the incidence of cancer in a cohort of women attending a large infertility clinic in the UK. The incidence rates of cancer of the breast, corpus uteri and ovary were not significantly different from expectation based on national cancer rates, and were similar for women who had received hormonal treatment to stimulate their ovaries and those who had not. These data do not support a hypothesis linking infertility treatment involving ovarian stimulation with increased breast, uterine and ovarian cancer over the follow-up period studied.

General and local examination detects adenexal masses, by which we may suspect the nature of mass but cannot prove or disprove cancer ovary. Examinations in addition to the other parameter of detection increase the suspicion of high risk cases for more evaluation.

CA125 is moste widely used indicator for detection and follow up of ovarian cancer. In this study CA125 more than 35 miu/dl has sensitivity of 88.3%, specificity 72.1%, positive predictive value

85.0%, and negative predictive value 77.5% with high significance.

With use of ***ultrasound*** by 2D VS 4D no significant difference in this study between both .by ultrasound with detection of solid / cystic ovarian masses, laterality (unilateral; bilateral), presence of septa , and papillae detection(internal or exteternal) were significant. The length of 10.5 cm , width of 9.5 cm ,and depth of 8.5 cm was detected to be of high significant in this study.

Menon et al. (7) mentioned that; The sensitivity for detection of ovarian cancer of different ultrasound criteria was 100% for abnormal morphology, 89.5% for abnormal volume and 84% for complex morphology. The highest specificity (97%) and positive predictive value (37.2%) was achieved using complex morphology.

Detection of neo-vascularization is one important subject for detection of abnormal tissue growth especially in the center of mass more than periphery of the mass. Detection of low resistance to blood flow and high pulsitility of blood flow toward the ovarian mass one of important item to suspect pathological lesion. PI of 0.86 has sensitivity of 90.9%, specificity 72.1%, positive predictive value 85.4%, negative predictive value of 81.6%; and RI of 0.51 has sensitivity of 84.4%, specificity of 72.1%, positive predictive value of 73.9%, and negative predictive value of 81.6%, and both were high significant in detection of malignancy.

Risk of malignant index is used for detection of ovarian cancer by certain equation which include menopausal status, ultrasound data, and CA125 value. By evaluation of risk of ovarian cancer in this study it has sensitivity of 84.4%, specificity of 44.2%, positive predictive value of 85.4, and negative predictive value of 61.3%; and was significant.

Jacobs et al. (8) mentioned that Age, ultrasound score, menopausal status, a clinical impression score and serum CA 125 level were assessed 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 RMT 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.

As regard, ***Zagazig ovarian cancer index*****,** by use of multiple variable which include:

1- CA 125 more than 35
2- PI more than 0.86
3- RI less than 0.51
4- length more than 10.5 cm
5- width more than 9.5 cm
6- depth more than 8.5
7- presence of solid area
8- bilateral
9- internal papillae
10- external papillae

We detect by certain equation with cut value of 1, if more than 1 the patient has cancer ovary, and with value of les than 1 patient has no cancer ovary and this by sensitivity of 90.9%, specificity 88.4%, positive predictive value 93.3%, and negative predictive value 84.4%. by this equation detection of ovarian cancer is highly significant more than any parameter

used alone and more than ovarian cancer malignant index.

CONCLUSION

1- Early detection of cancer ovary is applicable, but in challenge
2- Use of ovulation induction medication by specialists has no hazards effect for cancer ovary development.
3- Cigarette smoking (passive or active) detected to has no increased risk of cancer ovary
4- the use of risk of malignant index is valuable for detection of cancer ovary
5- the use of ultrasound data and Doppler study is valuable for detection of cancer ovary
6- Zagazig ovarian cancer equation has the most significance in early detection of cancer ovary

REFERENCES

1- **Wilson J and Jungner G:** WHO principles and practice of screening for disease. WHO 1968; 66-67.
2- **Parkin DM, Bray F, Ferlay J, et al.:** Global cancer statistics. CA Cancer J Clin 2005; 55: 74–108.
3- **Antoniou A, Pharoah PD, Narod S, et al.:** Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. Am. J. Hum. Genet. 2003; 72: 1117-1130.
4- **Burke W, Daly M, Garber J et al.:** Recommendations for follow-up care of individuals with an inherited predisposition to cancer. J. Am. Med. Assoc. 1997; 277: 997-10033.
5- **Baron AT, Lafky JM, Boardman CH, et al.:** Serum sErbB1 and epidermal growth factor levels as tumor biomarkers in women with stage III or IV epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev 1999; 8:129–137.
6- **Adam, B. L., Qu, Y., Davis, J. W., et al.:** Serum protein fingerprinting coupled with a pattern-matching algorithm distinguishes prostate cancer from benign prostate hyperplasia and healthy men. Cancer Res. 2002; 62: 3609 –3614.
7- **Menon U, Skates SJ, Lewis S, et al.:** Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. J Clin Oncol 2005; 23:7919–7926.
8- **Jacobs IJ, Skates SJ, Macdonald N, et al.:** Screening for ovarian cancer: A pilot randomized control trial. Lancet 1999; 353: 1207-1210.