INTRODUCTION

Gynecological malignancy arising from the ovary, cervix, endometrium, vulva or vagina affects about 2.2% of the females population by the age of 65; it is the second most common cause of cancer death in women following breast cancer ***(Ferlay et al., 2010).***

Each year, the American Cancer Society estimates the numbers of new cancer cases and deaths expected in the United States in the current year and compiles the most recent data on cancer incidence, mortality and survival based on incidence data. A total of 1, 596, 670 new cancer cases and 571, 950 deaths from cancer were projected to occur in the United States in 2011 ***(Siegel et al., 2011).***

Ovarian cancer is one of the deadliest cancers in women since it is often detected at an advanced stage, it occurs most frequently in women who are between 40 and 65 years of age and the lifetime risk of developing ovarian cancer is 1.4 to 1.8 percent for women living in the United States ***(Cannistra et al., 2004).*** Age specific incidence is 40/100, 000 by the age of 50 and rises to 50 per 100, 000 women by the age of 65 years, while malignant tumor of the ovaries occur at all ages with variation in histological sub-type by age ***(Jemal et al., 2011).*** The incidence of ovarian cancer is low in young women while the epithelial

ovarian cancers are not known to occur before menarche; most of them are germ cell tumor, juvenile granulosa cell tumor and serous borderline tumors ***(Jemal et al., 2010).***

It is the second most common female gynaecological cancer in the UK with 7100 new cases detected in 2011 meaning 19 women every day and the lifetime risk of developing the disease is 1 in 48 ***(Cancer Research, 2011).*** Ovarian cancer is the seventh most common cancer in women worldwide ***(Ferlay et al., 2012).***

The Epithelial ovarian carcinoma (EOC) is one of the top 10 most frequently occurring cancers in women with an estimated 22240 new cases in the United States in 2013 ***(Siegel et al, 2013).***

Annually in the US, approximately 21, 980 cases were expected to be diagnosed in the United States in 2014 with an expected 14, 270 deaths attributable to ovarian cancer ***(Siegel et al., 2014***).

The increase in survival rates can be attributed to the advances in surgical management, development of effective cytotoxic drugs and the intraperitoneal administration of chemotherapy so; ovarian cancer survival rates could also be improved through screening and early detection ***(Moore et al., 2010).***

Assays measuring tumor markers in serum or other body fluids have the advantage of being non invasive, simple to perform and relatively cheap. An acceptable screening assay would require a sensitivity of 75% and specificity of around 99.7% to obtain minimally tolerable positive predictive value of 10% for the detection of ovarian carcinoma ***(Hellstrom and Hellstrom, 2011)***.

AIM OF THE WORK

1- To compare between the Human epididymis protein - 4(HE4), Mesothelin, Vascular endothelial growth factor (VEGF) and CA125 in diagnosis and prediction of benign and malignant ovarian cancer in patients with adnexal masses.

2- To evaluate the utility of using a novel serum tumor markers as Human epididymis protein- 4 (HE4), Mesothelin and Vascular endothelial growth factor (VEGF) either alone or in combination with CA125 in diagnosis of benign and malignant ovarian cancer in patients with adnexal masses.

Chapter 1

OVARIAN CANCER

An adnexal mass:

In gynecology, the adnexa referred to the region adjoining the uterus that contains the ovary and fallopian tube; as well as associated vessels, ligaments, and connective tissues ***(Dearking et al., 2007).*** The mass in the adnexa may be symptomatic or discovered incidentally; some masses will regress spontaneously but others require a surgical procedure for histologic diagnosis and treatment ***(American College of Obstetricians and Gynecologist (ACOG), 2007***). Most adnexal masses may be characterized as benign or malignant on the basis of the clinical and ultrasonography findings ***(Mohaghegh and Rockall, 2012).***

An adnexal mass may be found in females of all ages, fetuses to the elderly, the reported prevalence varies widely depending upon the population studied and the criteria employed ***(Castillo et al., 2004).*** The normal ovary is approximately 3 cm in length but decreased in size after menopause, in some women, the ovarian cancer is initially suspected when a mass or lump is felt during a routine pelvic examination; however a mass is not always detectable in the early stages of ovarian cancer ***(Vanessa et al., 2009).***

Suspected ovarian neoplasm is a common problem in women of all ages, women have a 5 to 10 percent risk of requiring surgery, and those who undergo surgery have a 13 to 21 percent chance of being diagnosed with ovarian cancer so the primary goal of diagnostic evaluation of adnexal masses is to take into account the woman's age and family history ***(Graham, 2008).*** The guidelines for the management of adnexal masses included the patient factors, physical findings, imaging results, and serum markers that help to categorize masses to guide physicians in choosing the appropriate management strategy as seen in figure (1) ***(ACOG, 2002).***

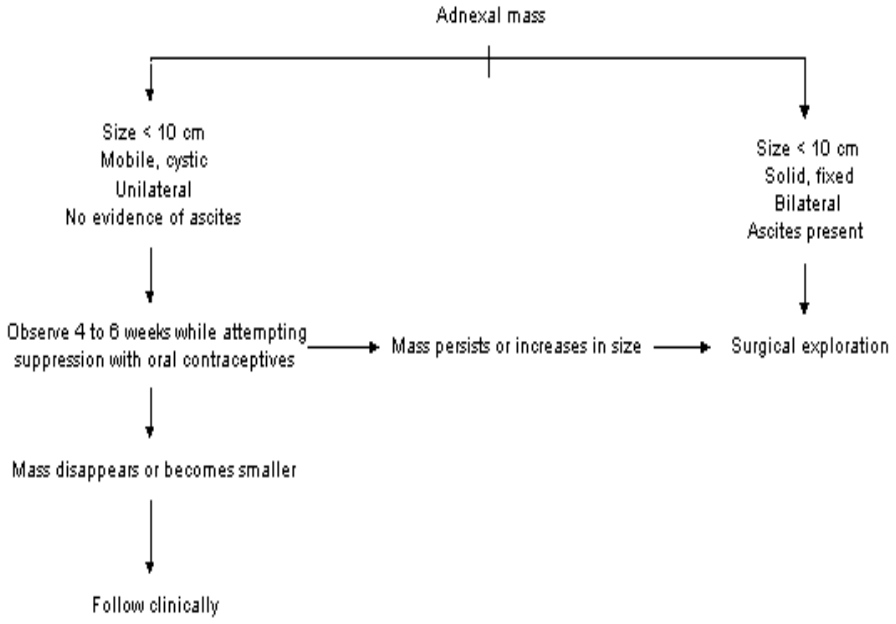

Fig. (1): Management of adnexal masses in premenopausal women.

The criteria for management pre and postmenopausal women with adenxal mass:

Premenopausal women:

CA 125 >200 U/mL, ascites, evidence of abdominal or distant metastases, family history first-degree relative(s) with breast or ovarian cancer.

Postmenopausal women:

Elevated CA 125, ascites, nodular or fixed pelvic mass, evidence of abdominal or distant metastases, family history first-degree relative(s) with breast or ovarian cancer ***(Demir and Marchand, 2012)***

Importance of discriminating benign from malignant masses:

The clinical significance of discriminating benign from malignant masses differs depending on the clinical setting in which the mass is initially detected in women who initially present with symptoms, the diagnosis of the underlying cause of the mass is important in treatment options. Although medical therapy may relieve symptoms in some cases but surgical management is the treatment of choice for many conditions ***(Munstedt et al., 2003).***

Because surgery may ultimately be the most appropriate management for symptomatic adnexal masses, the main reason to discriminate between benign and malignant lesions is to facilitate referral and management by clinicians with specialized training and experience in managing ovarian malignancy with improved outcomes ***(Tingulstad et al., 2003).***

Many asymptomatic women may have an adnexal mass detected during a periodic health maintenance examination so discriminating benign from malignant disease is important not only to ensure appropriate management in the setting of malignancy but also to avoid unnecessary diagnostic procedures, including surgery and anxiety in women with asymptomatic-nonmalignant conditions ***(Patel et al., 2006).***

Ovarian cancer:

Ovarian cancer is the leading cause of death from gynecologic malignancy in the United States ***(Siegel et al., 2013),*** most ovarian cancers are diagnosed at an advanced stage in which 5-year survival rate is approximately 30%, while it is greater than 90% in women diagnosed at an early stage ***(Su et al., 2013).*** Diagnosis of ovarian cancer is largely based on symptoms, imaging, and laboratory biomarkers ***(Lokshin, 2012).***

The prevalence of ovarian and paraovarian cysts is high in both peri- and post-menopausal women but it is benign in most

cases, also the hormonal changes taking place around the menopause may predispose the development of these benign ovarian cysts ***(Healy et al., 2008).*** American College of Obstetricians and Gynecologists in 2007 reported the management of ovarian cysts in postmenopausal women as represented in figure (2).

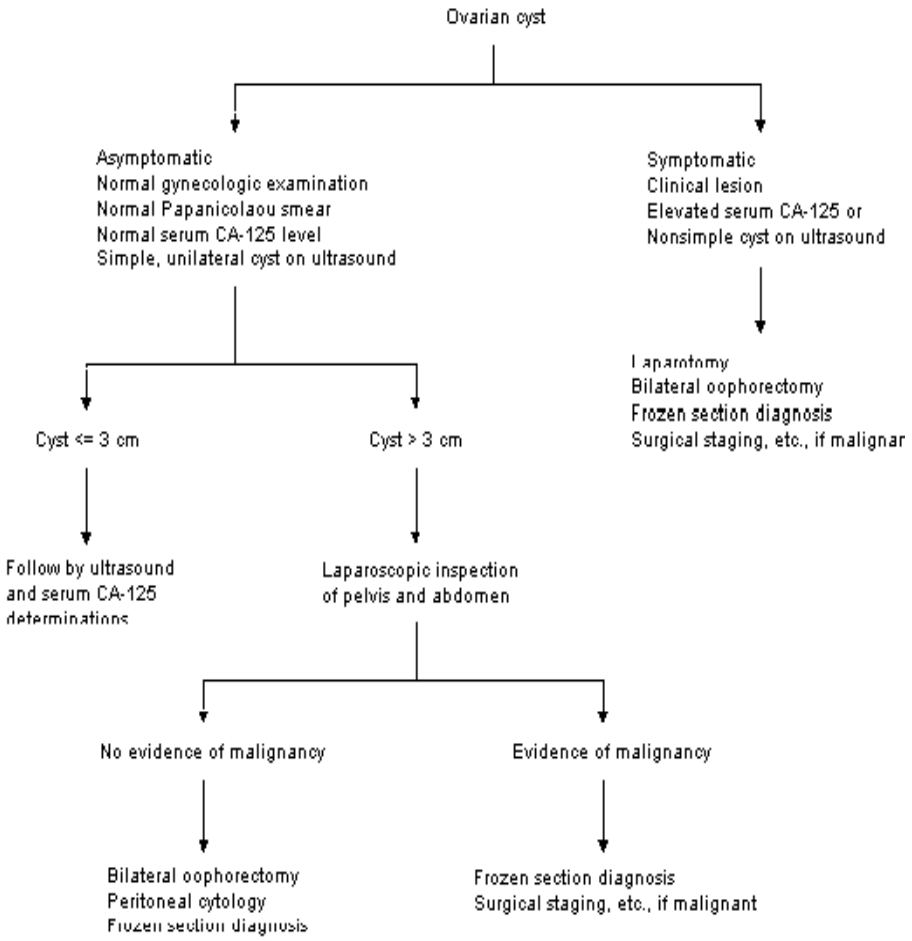

Fig. (2): Management of ovarian cysts in postmenopausal women.

The ovaries contain 3 main kinds of cells:

- Epithelial cells which cover the ovary.
- Germ cells which are found inside the ovary, it developed into the -ova which released into the fallopian tubes every month during the reproductive years**.**
- Stromal tumors start from structural tissue cells that hold the ovary together and produce the female hormones estrogen and progesterone, each of these types of cells can develop into a different type of tumor ***(Hennessy et al., 2009)***.

A- Ovarian cancer is classified according to the histology of the tumor into:

- **Epithelial tumors** which start from the cells that cover the outer surface of the ovary, most of these tumors are benign and can be treated by removing either the ovary or the part of the ovary that contains the tumor ***(Rossing et al., 2008).***
- **Sex cord-stromal tumor** which including estrogen-producing granulosa cell tumor and virilizing Sertoli-Leydig cell tumor, it accounts for 8% of ovarian cancers ***(Tavassoli et al., 2003).***
- **Germ cell tumor** which begins in the reproductive cells of the body and usually occurs in teenage girls or young

women and most often affect just one ovary ***(Pectasides et al., 2008).*** These tumors are frequently unilateral and are generally curable if found and treated early ***(Gershenson 1993)***.

- Mixed tumors containing elements of more than one of the above classes of tumor histology (***Kline and Bazzett-Matabele, 2010).***

I-Epithelial ovarian tumors:

i-Pathogenesis of epithelial ovarian cancer:

Epithelial cancer of the ovary derives from malignant transformation of the epithelium of the ovarian surface, which is contiguous with the peritoneal mesothelium ***(Cannistra, 2004).*** It is often described as the silent killer or the disease that whispers mainly due to absence of its symptoms and the lack of specific/sensitive markers and/or techniques of screening leads to the diagnosis at late stages of the disease in more than 70% of patients ***(Véronique et al., 2008).*** It is a complex disease stratified according to histopathological and morphological criteria, the majority of EOCs are thought to arise from the ovarian surface epithelium (OSE) that is derived from the coelomic epithelium ***(Fritz-Rdzanek et al., 2012).***

ii- Types of epithelial ovarian tumors:

1- Benign epithelial ovarian tumors:

Most epithelial ovarian tumors are benign, don't spread and usually don't lead to serious illness; there are several types of benign epithelial tumors including serous adenomas, mucinous adenomas and Brenner tumors (***Olsen et al., 2008).*** Benign serous tumors are unilocular or multilocular which contain clear fluid with a smooth lining composed of columnar epithelial cells with cilia and they are curative by surgery (figure 3) ***(Levanon et al., 2008).***

Mucinous tumors are part of the surface epithelial-stromal tumor group of ovarian neoplasms and account for 12-15% of all ovarian tumors (figure 4). Approximately 75% are benign, 10% are borderline and 15% are malignant while approximately 5% of primary mucinous tumors are bilateral ***(Hart, 2005).***

Fig. (3): Benign serous ovarian tumor.

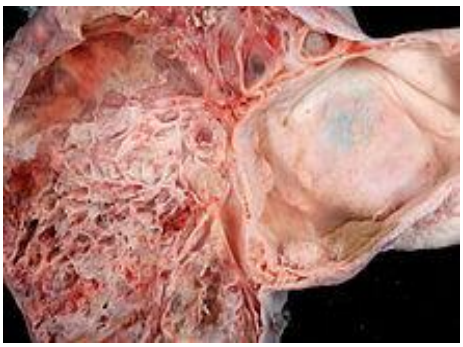

Fig. (4): Mucinous tumor of the ovary.

2-Tumors of low malignant potential:

Under the microscope, some ovarian epithelial tumors don't clearly appear to be cancerous so called tumors of low malignant potential (LMP tumors), they are also known as borderline epithelial ovarian cancer and affects women at a younger age than the typical ovarian cancers (***Kurian et al., 2005).*** Malignant epithelial ovarian tumors are called carcinomas and about 85% to 90% of ovarian cancers are epithelial ovarian carcinomas while the serous type is by far the most common one, but there are other types like mucinous, endometrioid and clear cell (figure 5) ***(Bell et al., 2004).***

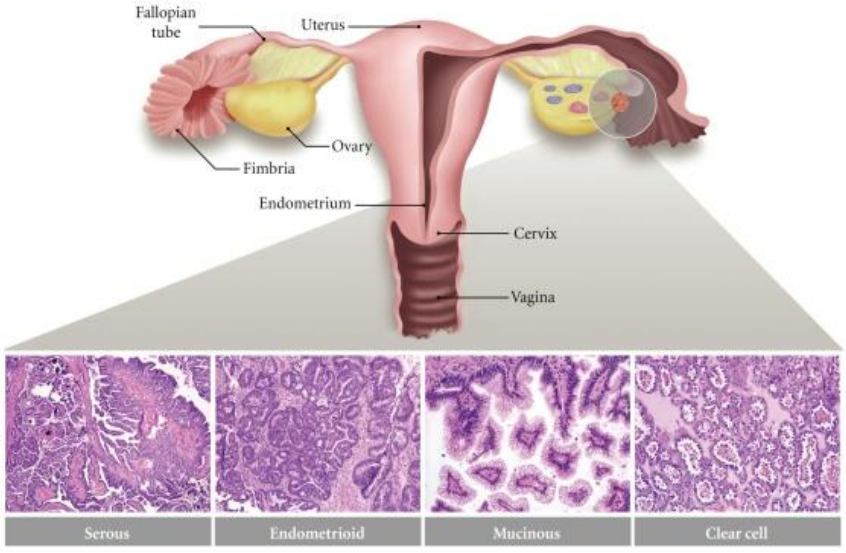

Fig. (5): The major histologic subtypes of ovarian carcinoma. Serous carcinomas resemble fallopian tube epithelium, endometrioid carcinomas resemble endometrial glands, and mucinous carcinomas resemble endocervical epithelium. Photographs show representative tumor sections stained with hematoxylin and eosin.

II- Germ cell tumors:

Germ cells tumors are the cells that usually form the ova, the most germ cell tumors are benign but some are cancerous and may be life threatening. There are several subtypes of germ cell tumors including teratoma, dysgerminoma, endodermal sinus tumor and choriocarcinoma (***Prat, 2004).***

1-Teratomas

Teratomas are germ cell tumors had a benign form called mature teratoma and a cancerous form called immature teratoma, the mature teratoma is the most common ovarian germ cell tumor. It is often called a dermoid cyst because its lining resembles skin; the immature teratomas are a type of cancer which occurs in girls and young women (figure 6) ***(Kim et al., 2009).***

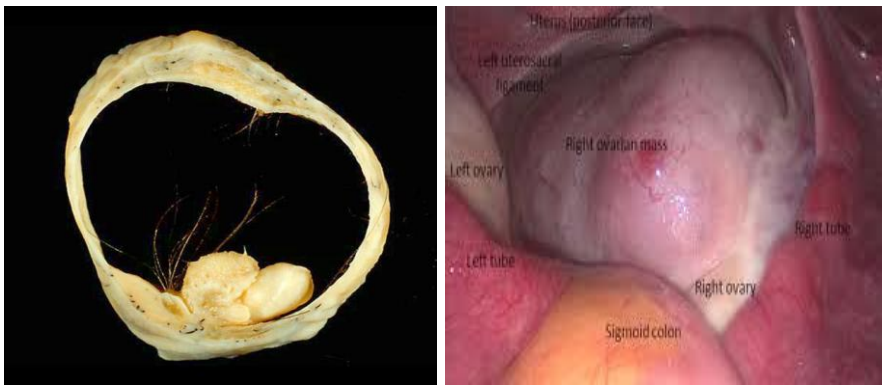

Fig. (6): Mature cystic teratoma of the ovary and ovarian mass.

2-Dysgerminoma

This is the most common ovarian germ cell cancer; it usually affects women in their teens and twenties and more than 75% of patients are cured by surgically removing the ovary without any further treatment. Even when the tumor has spread further surgery, radiation therapy, and/or chemotherapy are effective in controlling or curing the disease in about 90% of patients ***(Song et al., 2007).***

3-Endodermal sinus tumor (yolk sac tumor) and choriocarcinoma

It is rare tumors typically affect girls and young women; they grow and spread rapidly but are usually very sensitive to chemotherapy ***(Oh et al., 2001).*** Choriocarcinoma are tumors start in the placenta (during pregnancy) and usually respond better to chemotherapy than do ovarian choriocarcinomas ***(Motegi et al., 2007).***

III -Stromal tumors :

About 1% of ovarian cancers are ovarian stromal cell tumors and more than half of stromal tumors are found in women older than 50, but about 5% of stromal tumors occur in young girls. The most common symptom of these tumors is abnormal vaginal bleeding because many of these tumors