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A review : The Relationships Between Ovary Disease and Tumor Marker

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1-Introduction :

The ovary is an organ found in the female reproductive system that produces an ovum. When released, this travels down the fallopian tube into the uterus, where it may become fertilized by a sperm. There is an ovary found on each side of the body. The ovaries also secrete hormones that play a role in the menstrual cycle and fertility. The ovary progresses through many stages beginning in the prenatal period through menopause. It is also an endocrine gland because of the various hormones that it secrete. **[1]**

The ovary starts secreting more and more hormones at puberty. The hormones trigger the development of secondary sex traits. Starting with adolescence, the ovary undergoes structural and functional changes. The ability of the ovaries to control hormones makes them crucial to fertility and conception. A number of feedback mechanisms are stimulated when egg cells, or oocytes, are expelled from the Fallopian tube, which changes the hormone levels in the body. [2]

Ovaries release progesterone, estrogen, testosterone, and inhibin at sexual maturity. The adrenal glands and ovaries in women create 50% of the body's testosterone, which is then immediately delivered into the bloodstream. Estrogen is in charge of the maturation and maintenance of the reproductive organs in their mature functional state, as well as the appearance of secondary sex characteristics in females during puberty. The uterus and mammary glands are prepared for pregnancy and breastfeeding, respectively, by progesterone. Progesterone and estrogen work together to promote endometrial changes associated with the menstrual cycle. [3] [4]

The female gonads are regarded as the ovaries. The ovarian fossa, where each ovary is situated, is an area that runs along to the uterus' lateral wall. The area in front of the ureter and internal iliac artery, and bordered by the external iliac artery, is known as the ovarian fossa. This region measures roughly 4 cm by 3 cm by 2 cm. The ovaries have an outer cortex and an inner medulla, and they are encircled by a capsule. The tunica albuginea, which is the name of the capsule, is made of dense connective tissue. Each menstrual cycle, ovulation typically takes place in one of the two ovaries, releasing an egg. The infundibulopelvic ligament connects the side of the ovary closest to the fallopian tube to it, and the ovarian ligament connects the side of the ovary that points downward to the uterus. [5] [6]

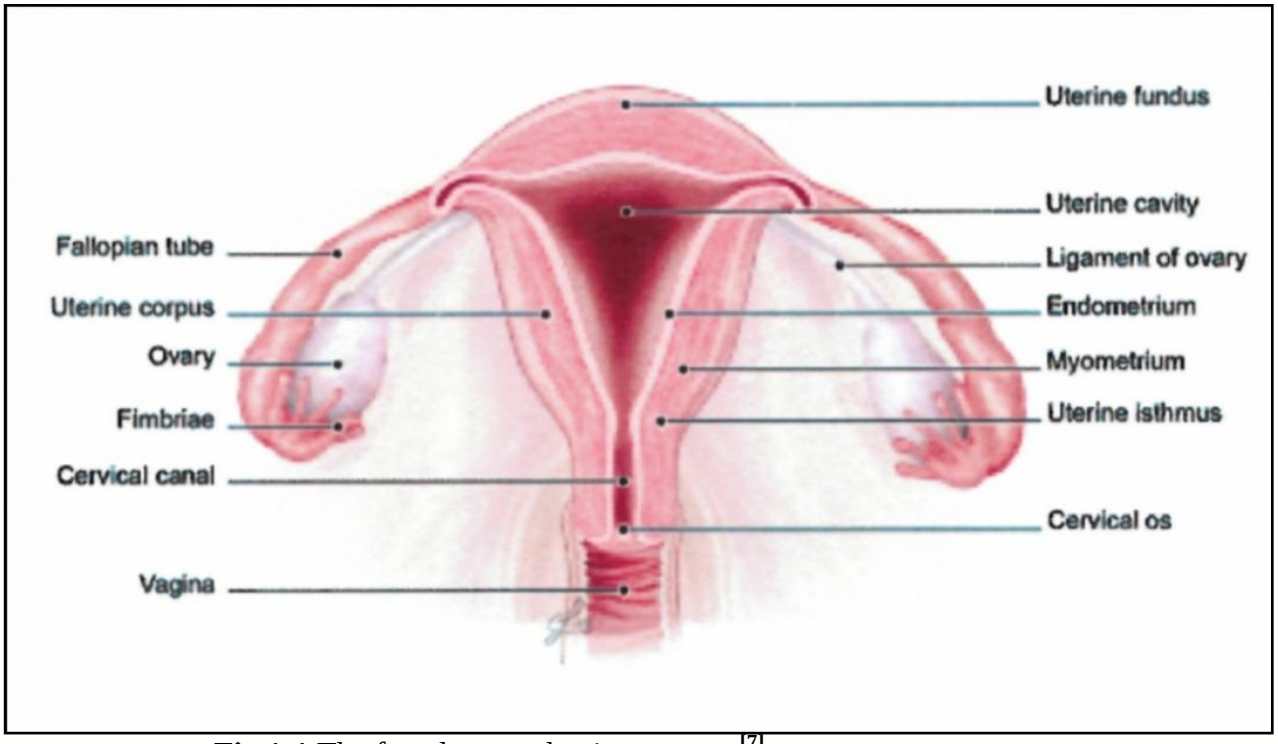

Fig 1-1 The female reproductive system. [7]

2- In this article, we discussed three types of ovarian diseases are:

1. ovarian cysts.
2. Polycystic ovary syndrome.
3. ovarian dermoid.

3- Ovarian cyst

An ovarian cyst is a sac that develops in the ovary and is filled with liquid or semiliquid material. The prevalence of routine physical exams and the use of ultrasound technologies has increased the number of ovarian cyst diagnosis. Women experience significant anxiety when an ovarian cyst is found because they worry that it might be cancerous, even though the vast majority of ovarian cysts are benign. From the neonatal period until the post-menopausal stage of life, these cysts can progress in females. Nevertheless, the majority of ovarian cysts occur during the hormonally active developmental years of childhood and adolescence. The majority are of a functional character and resolve on their own. Ovarian cysts, however, may signal an underlying cancerous process or, more likely, divert attention away from a more dangerous illness, for example, appendicitis, ovarian torsion, or ectopic pregnancy. (Conversely, there could be an inverse association between breast cancer and ovarian cysts). Once ovarian cysts are large, painful, persistent or have concerning radiographic or exam findings, surgery may be required, from time to time resulting in removal of the ovary. [8][9]

3_1_ Types of ovarian cysts:

There are several different types of ovarian cysts which include:

1-1-1Functional ovarian cysts : These cysts, which are the most prevalent kind, appear during the menstrual cycle. The subtypes of functional cysts include graafian (or follicular) cysts, which appear during the first half of the menstrual cycle, the corpus luteum, which appears during the second half of the cycle when the follicular cyst ruptures but does not disintegrate, and the hemorrhagic or blood-filled cyst, which appears when a blood vessel within a cyst breaks, causing the cyst to fill with blood. Hemorrhagic cysts typically go away on their own but may need to be surgically removed if they are painful and persistent.

1-1-2Pathological ovarian cysts : Examples of these cysts that develop as a result of cellular irregularity include dermoid cysts, which are benign tumors made up of bits of hair, fat, or bone, and endometrioid cysts, also known as chocolate cysts, which are brought on by endometriosis. [10]

3-2- Symptoms :

The majority of ovarian cyst patients are asymptomatic, and the cysts are typically found by chance during ultrasonography or a normal pelvic check. However, some cysts may be accompanied by a variety of symptoms, some of which may be severe, but malignant ovarian cysts typically do not present signs until they are well progressed. The lower abdomen may experience discomfort or worry. Pain that is more intense can result from torsion or rupture. Pelvic discomfort that is abrupt, unilateral, and severe is a sign of cyst rupture. This may be connected to trauma, physical activity, or coitus. Additionally, a ruptured cyst might cause self-limiting bleeding, peritoneal symptoms, and abdominal distention. [11]

-Other symptoms include the following:

Patients may feel uncomfortable during sexual contact, especially during deep penetration.- It may be difficult to urinate, or pressure may build up, making you want to urinate. Tenesmus may occur in some patients. Patients could feel bloated and full in the abdomen. Young children may have early menarche and precocious puberty. Patients may experience heartburn, indigestion, or early fullness. Because of the pressure on the bladder, frequent micturition may happen .[12]

A common clinical and ultrasound finding is an ovarian cyst. The majority of ovarian masses in premenopausal women and the majority of cysts found in postmenopausal patients are benign. In general, 1 in 1000 premenopausal patients and 3 in 1000 people over the age of 50 have a cancer. Patients are typically asymptomatic and incidental findings of ovarian cysts. One in every 25 women will experience symptoms from an ovarian cyst at some point in their lives. Once a cyst has been identified, it's critical to use transvaginal ultrasonography to categorize its characteristics. Management will be guided by this classification in conjunction with clinical characteristics like discomfort, pressure, or fertility. [13]

3-3 Diagnosis:

A normal pelvic check by the doctor can reveal an ovarian cyst. They might detect enlargement on one of the ovaries and request an ultrasound to see whether a cyst is present.

1. **Imaging tools used to diagnose ovarian cysts include:**

2. -**CT scan**: A body imaging device used to create cross-sectional images of internal organs.

3. -**MRI**: A test that uses magnetic fields to produce in-depth images of internal organs.

-Ultrasound device: An imaging tool used to view the ovary in order to assess a cyst's size, location, form, and fluid- or solid-filled composition.
The doctor might not immediately suggest a course of therapy because most cysts go away within a few weeks or months. To check the situation, they could perform the ultrasound examination once more after a few weeks or months.
The doctor will order additional tests to find alternative reasons of the symptoms if there are no changes in your condition or if the cyst grows in size.
These consist of:
- **Pregnancy test :** To make sure you're not pregnant.
- **Hormone level test :** To check for hormone-related issues, such as too much estrogen or progesterone.
- **CA-125 blood test :** To screen for ovarian cancer. [14]

3-4 Treatment :
Treatment will depend on :
The Watchful person's age.
- Whether they have undergone menopause or not.
- The size and appearance of the cyst.
- whether there are any symptoms.

waiting (observation):
Sometimes it's best to wait it out, especially if the cyst is small and functional (between 2 and 5 cm) and the lady hasn't reached menopause yet. A month or two later, an ultrasound will be used to check the cyst to see if it has disappeared.
Birth control pills:
The doctor could advise taking birth control tablets to lower the possibility of additional cysts forming in subsequent menstrual cycles. Ovarian cancer risk may be decreased with oral contraceptives.
Surgery:
Surgery may be recommended if:
- There are symptoms .
- The cyst is large or appears to be growing .
- The cyst does not look like a functional cyst .
- The cyst persists through 2 to 3 menstrual cycles.

Two types of surgery are:
1- Laparoscopy, or keyhole surgery: The cyst is removed by the surgeon through a very small incision using extremely little equipment. The patient can typically leave the hospital the same day. Fertility is typically unaffected by this kind of surgery, and recuperation durations are short.

2- Laparotomy: If the cyst is malignant, doing this can be advised. Across the top of the pubic hairline, a longer cut is created. The cyst is taken out and sent to the laboratory for analysis. Typically, a patient is hospitalized for at least two days. [15]

4- Polycystic ovary

The complex illness known as polycystic ovarian syndrome (PCOS) is characterized by high levels of testosterone, irregular menstruation cycles, and/or tiny cysts on one or both ovaries. [16] Polycystic ovaries are a physical or primarily biochemical manifestation of the illness (hyperandrogenemia). Anovulation, microcysts in the ovaries, suppression of follicular growth, and menstrual changes are all symptoms of hyperandrogenism, a clinical feature of PCOS. [17] At least 7% of adult women have PCOS, a diverse condition. [18]

According to research, PCOS affects 5% to 10% of females between the ages of 18 and 44, making it the most prevalent endocrine condition among American women of reproductive age. [19] Endometrial cancer, cardiovascular disease, dyslipidemia, and type 2 diabetes mellitus are more common in women with PCOS. [20]

Elevated levels of luteinizing hormone (LH) and gonadotropin-releasing hormone (GnRH), whereas muted or unaltered levels of follicular-stimulating hormone (FSH) are clinical indications of PCOS. The stimulation of the ovarian thecal cells as a result of the rise in GnRH results in an increase in androgen production. [21] FSH levels can be increased naturally or artificially to treat follicular arrest. According to several research, young girls who are nearing puberty and have a family history of PCOS are predisposed to the condition. Approximately 25% of people with PCOS have high prolactin levels. [22]

PCOS is a hormonal condition that has the potential to develop into a number of disorders. It is still a typical contributor to female infertility. Ovulation abnormalities, elevated androgen levels, and cystic ovaries are the three most typical causes of PCOS. Most women with PCOS experience ovulatory issues and high androgen levels. Additionally, high levels of androgen are directly linked to hirsutism, acne, and alopecia, and people with PCOS are more likely to have polycystic ovaries on pelvic ultrasound than the general population. [23]

4-1- Symptoms:

Menstrual abnormalities, infertility, signs of excess androgen, and other endocrine problems may be symptoms in women with PCOS. Traditionally, symptoms start to show up a few years after puberty. [24]

4-1-1 Menstrual Dysfunction:

Menstrual disruption in PCOS women might take the form of amenorrhea, oligomenorrhea, or episodic menometrorrhagia with related iron-deficiency anemia. Anovulation is typically the cause of amenorrhea and oligomenorrhea. [25]

4-1-2 Hyperandrogenism:

Clinical manifestations of the condition typically include hirsutism, acne, and/or androgenic alopecia. However, virilization symptoms including increased muscular mass, voice deepening, and clitoromegaly are not common in PCOS patients. A tumor of the ovary or adrenal gland that produces androgen should be investigated since virilization indicates increased amounts of androgen .[24]

4-1-3 Other Endocrine Dysfunction :

- **Insulin Resistance :**

The link between insulin resistance, hyperandrogenism, and PCOS has long been known, although not being fully understood. An old study showed that when compared to weight-matched controls without PCOS, both lean and obese women with PCOS have higher risks of insulin resistance and type 2 diabetes. [26] [27]

- **Acanthosis Nigricans :**

Thickened, gray-brown velvety plaques that are observed in flexure areas like the back of the neck, axillae, inframammary creases, waist, and groin are what characterize this skin disorder. Acanthosis nigricans should be a cutaneous indicator of insulin resistance, and it can occur in people with or without PCOS. [29]

- **Dyslipidemia :**

Increased levels of LDL and triglycerides, increased total cholesterol:high-density lipoprotein (HDL) ratios, but decreased HDL levels are all characteristics of the classic atherogenic lipoprotein profile seen in PCOS. [30]

- **Obesity :**

Women with Pcos are more likely to be obese when compared to controls of the same age, as shown by elevated BMIS and waist:hip ratios. [31]

4-1-4 Obstructive Sleep Apnea :

Insulin resistance and central obesity are likely related to the disorder. [32] [33] When compared to weight-matched controls, women with Pcos have a 30- to 40-fold higher chance of developing sleep apnea. [34]

4-1-5 Metabolic Syndrome and Cardiovascular Disease :

Insulin resistance, obesity, atherogenic dyslipidemia, and hypertension are the hallmarks of the metabolic syndrome. It is linked to a higher risk of type 2 diabetes mellitus (DM) and cardiovascular disease (CVD). [35]

4-1-6 Endometrial Neoplasia :

The risk of endometrial cancer is tripled in women with PCOS. Chronic anovulation raises the risk of endometrial cancer and endometrial hyperplasia, and persistent unopposed estrogen is thought to be the cause of neoplastic alterations in the endometrium. [36]

4-1-7 Infertility :

Infertility or subfertility is a common complaint among PCOS sufferers who experience irregular menstrual periods. Furthermore, PCOS is the most prevalent cause of infertility among women whose anovulation-related infertility. [37]

4-1-8-Pregnancy Loss :

Compared to a baseline rate of about 5% in the general population, women with PCOS who become pregnant face an increased rate (30 to 50%) of early miscarriage. [38] [39]

4-1-9-Complications in Pregnancy :

PCOS has been linked to several pregnancy and neonatal problems. According to a significant meta study, males with PCOS are two to three times more likely than women without PCOS to experience gestational diabetes, pregnancy-related hypertension, preterm birth, and perinatal mortality. [40]

4-1-10 Psychologic Health :

Numerous psychological issues, including anxiety, despair, low self-esteem, a poor quality of life, and negative body image, might be present in women with PCOS. [41][42]

4-2 Diagnosis :

National Institutes of Health Criteria (NIH), developed in 1990, only need the presence of clinical and/or biochemical hyperandrogenism and oligo/amenorrhea anovulation as diagnostic criteria for PCOS. [43] Later in 2003, the Rotterdam Criteria added a third criterion to the two NIH criteria by using the ultrasound appearance of polycystic ovarian tissue. The diagnosis of PCOS was expanded by the Rotterdam consensus of the European Society of Human Reproduction and Embryology and the American Society for Reproductive Medicine (ESHRE/ASRM), which required two of the three features of anovulation or oligo-ovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovarian morphology (PCOM) as seen on ultrasound. Finally, the Androgen Excess Society defined PCOS as hyperandrogenism along with polycystic ovaries or ovarian dysfunction. The Androgen Excess Society (AES) stated that androgen excess should be present and accompanied by oligomenorrhea, PCOM, or both of them since it believed that androgen excess is a critical event in the development and pathogenesis of polycystic ovarian syndrome. [23]

Other androgen excess disorders should be ruled out, including drug-induced androgen excess, Cushing's syndrome, androgen-secreting tumors, hyperprolactinemia, thyroid disorders, non-classical congenital adrenal hyperplasia (NC-CAH), androgen-secreting tumors, hyperprolactinemia, and thyroid diseases. [44]

4-3- Treatments :

At the moment, PCOS is the most common factor in women's menstrual difficulties. Clinical and/or biochemical hyperandrogenism, abnormal ovulation, and the presence of enlarged and/or polycystic ovaries on ultrasound pictures (ovarian volume > 10 mL and/or 12 or more tiny bubbles distributed circumferentially) are its defining characteristics. It is a risk factor for the emergence of diabetes and cardiovascular diseases (CVDs) and frequently coexists with hyperinsulinemia, dyslipidemia, overweight, or obesity. The predominant symptoms will determine how PCOS patients are treated. [45]

The methods used to treat PCOS are generally determined by the desired therapeutic outcome, which may include infertility therapy, menstrual cycle regulation, relief from hyperandrogenism symptoms, or weight loss treatment. Clomifene is still the first-line treatment for females who want to get pregnant. It is an estrogen receptor modulator that quickly and effectively impacts the hypothalamic-pituitary axis; 75% of pregnancies among clomifene users occur during the first three months of medication. Metformin is another medication used with PCOS individuals looking to regain fertility; results are seen after 6 months of treatment. [46]

It is still debatable how much metformin contributes to ovulation induction. Metformin helps to lower insulin and testosterone levels, which helps to restore the regularity of the ovulatory cycle and periods. A biguanide derivative known for many years, metformin not only lowers blood pressure and insulin resistance, enhances lipid profiles and antioxidant properties, and raises levels of sex hormone binding globulin (SHBG), but it also works to protect the cardiovascular system through its pleiotropic

effect on the vascular endothelium. [47] Additionally, various writers have reported on its dose-dependent preventive impact against the risk of developing endometrial, breast, intestinal, and hepatic cancer. [48]

Despite the claims of many experts, metformin does not appear to have any effect on body weight reduction. Instead, the only association that might exist is the shift of active visceral fat to inactive subcutaneous fat, according to a recent study. [47]

5- Dermoid cyst

The most frequent germ cell tumors of the ovary include ovarian dermoid cysts. Although they are nearly always benign, 2% of them have been documented to undergo malignant transformation. Eighty-eight percent of instances are unilateral, and eighty percent of those cases are discovered during the reproductive phase. Dermoid cysts make about 35-58% of benign tumors but only 27-44% of primary ovarian cancers. The rise of the aforementioned tumor markers may also be related to benign ovarian diseases. [49]

Dermoid cysts are the most frequent ovarian mass to develop in children, according to the authorities [50][51]. They are also the most common solid type malignancy. Somatic malignant transformation leads to mature cystic teratoma with malignant degeneration. Age over 45, cyst size greater than 10 cm, rapid growth, and aberrant sonographic and Doppler findings such as enhanced vascularity, hetero echo pattern, papillary projections, and septation are all characteristics that raise the risk of dermoid cyst malignant transformation.

5-1-Symptoms :

The sources state that [52][53] dermoid cysts are asymptomatic. Pelvic pain, which is mainly caused by ovarian torsion, affects 3% to 4% of women. Dermoid cysts have the highest incidence of torsion among ovarian cyst cases. The high fat content, its weight, and its lengthy pedicle are the most likely causes of this tendency. Torsion complicates nearly all dermoid cysts, including those that are not particularly large (more than 5 - 6 centimeters). Thus, this problem can be avoided by cystectomy of dermoid cysts larger than 5 cm. Ovarian torsion can cause ovarian loss or rupture (rare and fistulization). Laparoscopy and detorsion for individuals who are of reproductive age and oophorectomy for postmenopausal women are the preferred treatments for ovarian torsion.

5-2- Diagnosis:

An adult cystic teratoma, also known as a dermoid cyst, is a benign tumor that most frequently affects young females. Sonography of the pelvis is done initially. The major objective of sonography is to assess the likelihood of cancer in ovarian masses and dermoid cysts. Characteristic sonographic findings are present in 75% of cases. A dermoid cyst may occasionally be incorrectly thought to be cancerous. Clarifying some clinical aspects of dermoid cyst care was the goal of this review. [55]

An uncommon benign cystic teratoma called a dermoid cyst. It shows a variety of sonographic signs on ultrasonography because it often contains contents of ectoderm, mesoderm, and endoderm origin. It manifests as various zones of echogenicity because the dermoid cyst's lumen is typically filled with a combination of materials with ectoderm, mesoderm, and endoderm origins. The formation of globules from the hyperechoic fat within the hypoechoic fluid matrix, giving the strange look of "Coins in a Sack" on ultrasound. [56]

This sign is the only ultrasonographic indication of a dermoid cyst in 16% of instances. When the entire cyst is affected, the acoustic shadowing caused by the hyperechogenicity of the cyst's internal structures may be extensive, or it may only affect a small portion of the cyst. There are hyperechoic structures without a distal acoustic shadow in only 8% of dermoid cysts. [57]

5-3-Treatment :

Laparoscopy or laparotomy is the best surgical option for dermoid cyst therapy. Laparoscopy has been shown in numerous studies to be more effective than other surgical options for treating dermoid cysts. The laparoscopic approach is thought to be the best surgical technique for treating dermoid cysts. Less bleeding, less postoperative discomfort, less need for postoperative analgesics, a shorter hospital stay, less adhesion development, better cosmetic outcomes, lower total cost, and greater magnification are benefits of the laparoscopic method to dermoid cyst therapy. Compared to a lengthy procedure, the laparoscopic technique has the following drawbacks:

The risks associated with laparotomy include a higher rate of spillage, a higher rate of recurrence, higher individual costs, and a higher risk of surgery specific to laparoscopy. When should dermoid patients consider laparotomy, increased risk of surgery unique. **[58]**

6- In this article discuss the two tumor marker are (CA-125 and CA 19-9)

A surface antigen called CA 125 (Cancer/Carbohydrate Antigen 125) is primarily expressed by ovarian cancer cells. As a result, it is frequently utilized as a tumor marker to identify and track the development of certain tumors. Additionally, cells from a variety of organs, including the pleura, pericardium, Mullerian epithelium, peritoneum, etc., express CA 125. The goal is to determine the various factors that contribute to CA 125 elevation and to calculate how much CA 125 is elevated as a result of ovarian and non-ovarian sources. [59] A member of the mucin (MUC) family of high molecular weight glycoproteins, CA 125 is protective in nature and is encoded by the MUC 16 gene. Its purpose is to provide lubrication and maintain hydration on the luminal surface of epithelial cells. A tumor antigen called CA 125 is well-known for its use in the diagnosis of ovarian malignancies because it is expressed on the surface of ovarian cancer cells. Additionally, it aids in tracking the development of such malignancy. [60]

In reaction to mechanical stress or inflammation, the soluble glycoprotein CA 125 is cleaved by proteolytic enzymes and released from the cell surface into the blood or other bodily fluids such as pleural fluid (as in pleural effusion), peritoneal fluid (as in ascites), etc. [61] It is a large membrane-bound MUC that is generally expressed by cells in a variety of tissues, including the Mullerian epithelium, pericardium, pleura, and peritoneum (all are derived from ceolomic epithelium). [62]

Originally, it was thought that CA 125 was a particular tumor marker for ovarian cancers. MUC16 thus plays an important role in at least some of the adenocarcinomas of the GIT and its elevation suggests poor survival in such patients, according to recent studies, which also found detectable levels in the blood of patients with non-ovarian malignancies like colorectal adenocarcinoma, pancreatic, and gastric carcinoma.[63] Several studies have also revealed elevated levels of this biomarker in infectious diseases like tuberculosis and benign disorders like liver The necessity to assess and contrast the levels of CA 125 in different etiologies was necessitated by the

increased levels that were observed even in physiological situations like pregnancy. [64]

A monosialoganglioside known as CA-19-9 antigen is released by mucinous tumors of the digestive tract, such as those of the pancreas and biliary tree. [65] In addition to many benign disorders, high levels of the CA-19-9 antigen can be found in a variety of malignancies, such as epithelial ovarian carcinoma, colorectal carcinoma, and pancreatic adenocarcinoma. However, significantly elevated levels of greater than 10,000 U/ml were almost always found in malignancies that were in an advanced state. In this case report, a benign ovarian cyst and an excessively high CA-19-9 level are linked. [66]

The tetrasaccharide carbohydrate tumor marker CA 19-9, also known as carbohydrate antigen 19-9 or cancer antigen 19-9, has been suggested as a predictive biomarker in patients with pancreatic cancer. [67] However, CA 19-9 has also been identified in a variety of benign conditions, including diverticulitis, pancreatitis, bile duct obstruction, liver cirrhosis, heart failure, and hepatobiliary, colorectal, gastric, and lung cancer. [68] There are occasional examples of high CA 19-9 levels in ovarian cancer and benign ovarian masses in the literature, despite the fact that it is frequently used as a tumor marker in the aforementioned non-gynecological disorders. [69][70].

explained Many people with straightforward ovarian cysts identified by ultrasonography don't need to be treated. A chronic simple cyst with a diameter of less than 10 cm in a postmenopausal patient who has a normal CA125 result can be followed up with regular ultrasonographic exams.

[71] shown Increasing CA125 levels, larger or more complex cysts, or a 50% resolution rate for asymptomatic cysts under 5 cm may necessitate surgery. The probability of a malignant ovarian tumor increasing from 13% in premenopausal females to 45% in postmenopausal patients makes follow-up care crucial. [72] demonstrated that CA-125 was increased and CA 19-9 was normal in mature cystic ovarian tissue. In the cases with high reported values, tumor markers in ovarian cyst CA 19-9 levels were discovered (CA 19-9). When we looked at the tumor markers in our study, we discovered that the levels of CA 125 sensitivity, which is crucial for the detection of epithelial ovarian neoplasms in ovary cysts, were high. increased levels of CA-125 in women with cysts greater than 5 cm were [73] [74]explained. Patients with ovarian cancers had significantly higher CA 125 levels and older ages. [75] [76] which revealed that women with polycystic ovary syndrome had higher serum CA-125 levels. [77] Their study's findings demonstrated that there was no discernible change in the mean CA125 value between the PCOS group and the control group. [78] revealed that polycystic ovary syndrome had a mildly higher Serum CA19-9 level (PCOS.(

Dermoid cyst in Results of the examination of the CA-125 tumor marker were normal, as shown by [79]. [49]showed in their research that women with dermoid cysts had high levels of CA 19-9. also revealed elevated CA -125 levels.

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