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Natural History of Ovarian Cancer

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Abstract

Ovary cancer is a fullness paradigms disease and serious health problem Is important knows it's natural history, because has multi-factor origins, and understood it's behavior since risk factors until patient's dead, metastatic disease in patient is reality to challenger for oncology group. Ovarian cancer screening is today difficult theme; almost patients with disease had advanced ovarian cancer in the first visit with oncology. In this work we made a bibliographic report about natural history, is an analytic review that's brings up concepts since etiology theirs risk factors, evolution sources, preclinical horizon, clinical disease and related symptoms, without treatments, until host dead.

Keywords: Natural history; Ovarian cancer; Systemic chemotherapy

Introduction

Ovarian cancer (Ca ovary) is the 6th most common tumor in women. Worldwide more than 200,000 new cases are diagnosed each year are around 4% of all cancers diagnosed in women and 6.6 new cases per 100,000 women per year [1,2]. Its history is known scientifically for more than 150 years; where has not changed their mortality, and Yes, its incidence; the first thing despite treatments today highly expensive and sophisticated. In the last two decades there were only small improvements in the overall 5-year survival, while the 5-year survival has been increased, from 30% to 50% with the use of cisplatin; in total only 5% from 20% to only 25% in women with advanced tumors. In Europe, more than one third of women with ovarian Ca, living 5 years after their diagnosis [3]. Poor survival is in relation to the diagnosis founded in advanced stages of the disease [4]. It is a neoplasm that responds well to systemic chemotherapy more than 80% of the cases, when it is accompanied by optimal cyto-reductive surgery [5]. Despite complete response (CR) with first line chemotherapy (QT), ovarian epithelial cancer type presents recurrence in more than 50% of women.

It is the most common malignancy after cancer of the breast in women over 40 years old, occupies in developed countries, in Mexico occupies fourth place in deaths with gynecological tumors [6]. Epithelial ovarian cancer occurs in about 90% of cases and only 10% corresponds to the originated from germ cells. Approximately 75% to 80% of cases of ovarian epithelial histological type are serous, less common the mucinous, endometrioid, clear cell, Brenner and lineage cancers are undifferentiated [7] (Figure 1-Ca ovary according to its origin).

The majority of women with ovarian Ca are diagnosed with locally advanced disease and metastatic according to the International Federation of Gynecology and obstetrics (FIGO) clinical stages III or IV [8].

Stages according to the FIGO

Stage III: Tumor involves one or both ovaries with peritoneal implants positive outside the pelvis, or nodes of retroperitoneal or inguinal positive. Superficial liver metastasis. The tumor is limited to the true pelvis but with malignant extension verified histopathological in small bowel or omentum.

Stage IV: Tumor invades one or both ovaries with distant metastases. Pleural effusion liquid positive for histology, condition to hepatic parenchyma.

Development

Its origin has not really been clarified and there are multiple causes that have caused any number of medical publications in indexed and non-indexed journals. Ovary Ca is a disease belonging to the Group of them chronic and degenerative with a wide natural history. After 10 years of your control can again appear with fatal relapse in a short time. Perhaps the critical period to establish prognosis of survival and a long disease-free period, are the first 2 years after diagnosis; in locally advanced stages. Breast cancer, appears in two periods of life, young people in the first and in the second postmenopausal life.

Epithelial ovarian cancer, the most frequent of them, occupies the 3rd place of gynecological malignancies worldwide; in 2008, half of the new cases were presented in highly developed countries [9], in our country, Mexico, more than 4,000 new cases were recorded and as cause of death occupies until 2003, the 4th causes in women, being its diagnosis of the 50 to 70 years of age, in locally advanced stages [10]. 80% of the cases respond to primary treatment, although they have a high percentage of relapses, between 60 to 70% of cases as a result of the lack of appropriate research methods, favored by low symptoms and the lack of early-stage screening techniques that hinder the only curable [6] timely diagnosis. The presence of any pelvic tumor, recommendations have been published for the index of risk of malignancy for tumor of the ovary (RMI I), described by Jacobs in 1990, used the report of Immunohistochemistry of CA-125, ultrasound (US) which is expressed with a score of 0 to 3; menopausal status: 1, to pre-menopausic status, and 3, to postmenopausal women. This index has a sensitivity of 85% and a specificity of 97%. In 1996, Tiangulstad devised a variation to the Jacobs score, with his RMI I, named index of risk of malignancy, RMI II; Unlike RMI I, which has values of menopausal and 1-4 pelvic US from 1 to 4 of values; both with the sum of>200 as the level of Court [11]. Survival is influenced by the volume of the tumor. From 1975 to 2004, with optimal surgery and better chemotherapy at time,

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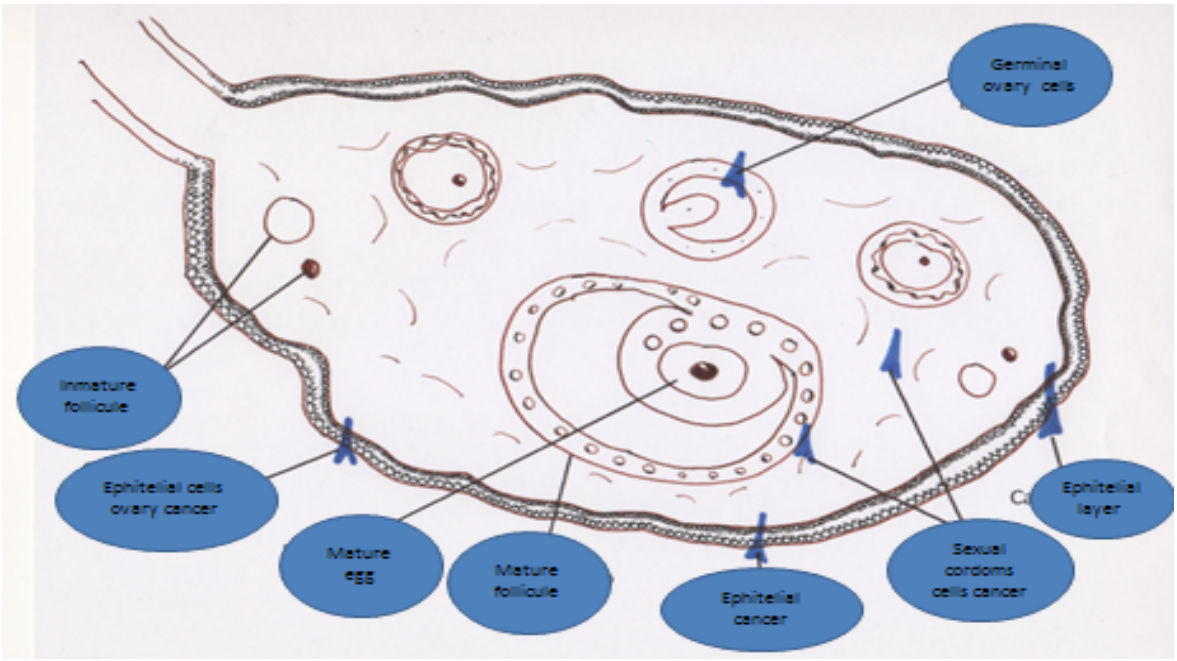

Figure 1: Ovaries cancer kinds, according Origen cells.

reached a median overall survival between 2 to 5 years and relapse after his survival not exceeded 2 years [12]. Large clinical studies published in the past 15 years, reveals that the median survival of patients with advanced disease (SLP) progression-free, oscillates between 16 and 23 months, while the median of SC is located between the 31 and 65 months [13]. Until QT with cisplatin, has been little improvement in treatments, survival rates haven't improved substantially, with the need for improved treatment regimens; It is the idea that target may be the use of agents anti-angiogenic treatments for Ca epithelial ovarian.

Inheritance for Ovarian Cancer

Alterations to the ovary Ca are transmitted in mitosis from one cell to another, but are not transmitted from parents to children, so there must be a predisposition or susceptibility to mutation in the germ line or a hereditary susceptibility. The cause and mechanism of hereditary cancer is the father's sperm, inherited individual becomes carrier and transmitted it to their offspring, according to the Mendelian laws, depending on the dominant or recessive character of altered gene that causes cancer. Usually, it is dominant gene; but, it is an oncogene and is recessive, is a mutated gene entities. The best known hereditary cancer is in breast, has this character of a 5% to 10% of cases. Its main cause is the mutation of the genes of chromosome 17 BRCA1 or BRCA2 oncosupressors from 13. The first of these genes is expressed in breast and ovarian cancer, because it is a gene entities, hereditary transmission is generally due to a mutant allele, which only manifests in the daughter, developing a tumor. The presence of abnormal BRCA1 is associated in women 50% to 80% probability of developing breast cancer and a predisposition to cancer of ovary [14].

Hereditary risks

- Mutations in BRCA 1 and BRCA 2-risk for Ca ovary of 27%-44%, compared to 1% of the general population.
- Syndrome mama-ovary-risk of 10%-44%.
- Li-Fraumeni syndrome.
- Lynch-risk syndrome of 9%-12%.
- Jewish Ashkenazi population-risk of 16%-60%

The Risk factorsof Ca epithelial ovarian is been in peri-menopausal women and postmenopausal [15,16]. Its frequency increases as the number of decades, are the most common factors:

1. A family history with Ca ovary.
2. Medium- high socioeconomic level, especially in industrialized countries.
3. Null parity, infertility and the use of stimulant medications of ovulation [17].
4. White race.
5. Fat diet and obesity.
6. Polycystic ovaries (Stem-Leventhal syndrome) [18].
7. Personal history of Ca breast, colon and endometrial (hormone-dependent tumors).
8. Exposure to asbestos, talc or radiation.
9. Migration of border cells (Figure 2) [19].
10. Low concentration of selenium joined proteins.

This last, the expression of selenium attached to proteins in the ovary, there is an overexpression of epithelial cells of the gonad, compared with overexpression to have neoplastic cells of the ovary, it was lower than in normal epithelial cells [20].

Ovary cancer biochemistry

Polycystic ovary syndrome is a genetic disorder, heterogeneous type, wrapping endocrine and metabolic problems, occurs most

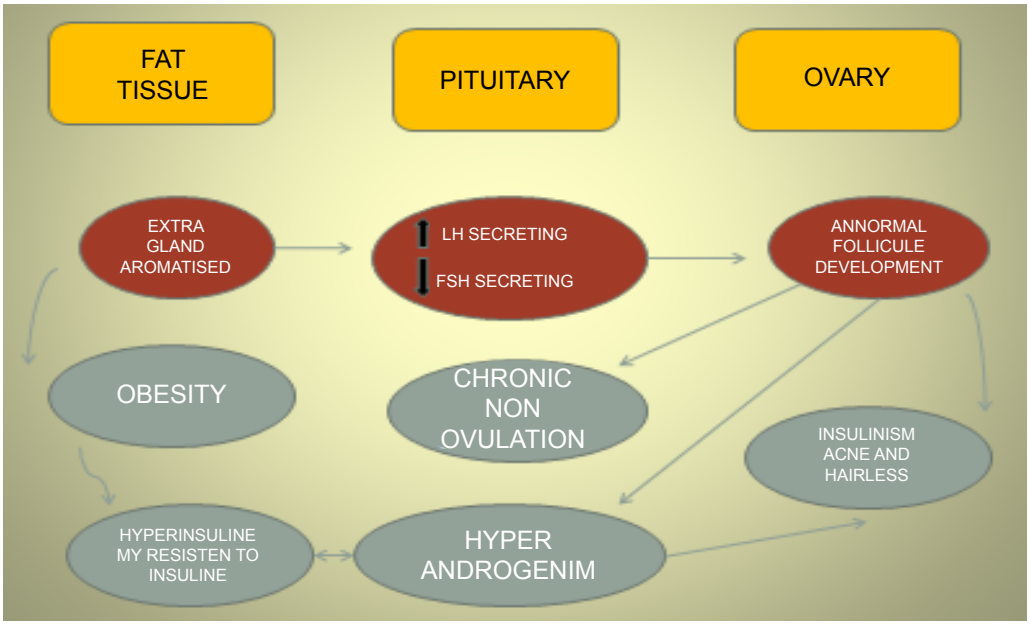

Figure 2: Migration of borderline cells.

often in women of reproductive age, characterized by an increase in the concentration of circulating androgens in the blood. With negative effect in normal functions of the metabolism. Policyst ovary syndrome can be changed to a metabolic syndrome, in the economy of the body. Showing marked synthesis of insulin in blood, abdominal obesity, increased blood pressure, dyslipidemia, insulin resistance, type 2 diabetes mellitus, cardiovascular disease with endometrial hyperplasic. Also, there are changes in the regulation in release of the gonadotropic hormone (HGC), this causes a disorder of feedback or *feedback* inhibition of steroid of the ovary. As a result the secretion of (LH) lutheotrofichormone increases in the body of the woman. Increases the secretion of (FSH), follicle-stimulating hormone; There is a hyperactivity of the stroma and the teak of the ovary cells, this result, there is an increase production of androgen secretion; all the above enables the presence of abnormalities in the biochemistry of the body's metabolism after menopause. There are several pharmacological therapies for PCOS from changes in the lifestyle, as diets of reduction, physical exercise, steering with nitrous-Dimethylamine production and increasing the metabolism of the ovary, reacting with the proteins present in them. Nitrous-dimetlamine is metabolized in the ovaries by mitochondrial and microsomal enzyme system. Microsomes and mitochondria cause the degradation of the nitrous-dimetlamine in the ovary become this toxic reactive metabolites and formaldehyde. Both come together in covalent bonds to proteins of the ovary, most of this degradation is performed in microsomes. When the DNA of normal epithelium of the ovary was separated and analyzed by Immunohistochemistry tests, this show altered sequences of bases of the acid deoxirribonucleic. These changes are due to toxic effects of reactive metabolites of nitrous-dimethylamine in the DNA, the normal cells of the epithelium of the ovary. This route can occur in women exposed to the consumption of tobacco or alcoholic beverages [21].

No hereditary factors

- Age>45 years
- Early menarche-relative risk, RR 1.0 (95% CI 0.6-1.3).
- Late menopause.-RR 2.5 (95% 1.1-5.8)
- Null parity.-pregnancy reduces the risk of Ca ovary (OR 0.78 for every pregnancy to term; the parity has a 1.7 RR (95% CI 1.1-2.8))
- Personal history of breast cancer.
- The use of clomiphene citrate treatment for sterility without pregnancy to term is associated with a RR of 2.3 (95% CI 0.5-11.4) compared with infertile women who do not use it.
- Obesity-RR 2.05, in women with a high BMI>30, after 18 years.
- Use of hormone replacement therapy>5 years.-RR 1.5 (95% CI 0.9-2.6).
- Smoking-OR 1.0
- Use of talc and asbestos exposure-daily use of talc RR 1.3 (95% CI 0.8-1.9).

Family factors risks (9% of the cases)

- Two relatives in 1st grade with breast or ovary cancer and one<50 years at the time of diagnosis, OR 2.90 (IC 95%, 1.92-4.36).
- A family member with breast unilateral cancer<40 years; bilateral, <30 years OR 1.35 (IC 95%, 1.03 - 1.78).

The clearly established protective factors include:

1. More than one pregnancy carried to term
2. Use of oral contraceptives and the maternal breast feeding; related to incessant ovulation.
3. Not well shown tubal occlusion.

Lynch II syndrome: It includes Ca not polipoid colorectal, endometrial cancer, high digestive, urothelial cancer of the renal pelvis, ureter, the ovary cancer [22,23] has been published that oral contraceptives can reduce the risk of Ca ovary above all on those who

are carriers of BRCA mutations, related also to the time of use, 20% for every 5 years of use of oral contraceptives [24].

Search for: There isn't until today an appropriate screeningprogram, for timely diagnosis, methods are expensive and no means will be diagnose malignant neoplasms at early stages of the disease. In the majority of cases, ovaries tumors are diagnosed in locally advanced stages or metastatic disease with a poor survival prognosis. However, in those with risk factors for inheritance or found in the directed anamnesis, is accepted to carry out studies of Immunohistochemistry with tumor markers. Don't forget the study *sinequanon* for suspected adnexal tumor, as pelvic US, preferably with Doppler color and better still vaginally in the early stages. The above described, hasn't impacted significantly statistics of survival prognosis in women with ovarian ´cancer. Women with high risk factors and satisfied parity, must be submitted before 35 years old to prophylactic salpingo-oophorectomy, without removing the possibility of a future developing carcinomatosis peritoneal, similar to advanced ovarian cancer. The deprivation of hormone replacement therapy in postmenopausal women isn't statistically improved survival of the ill with ovarian canceror other gynecological neoplasmsdon't used, has favored cardiovascular ischemic events and loss of bone mass by its absence.

Diagnosis

Almost, ovary cancer is manifested by the increase in volume of the abdomen, symptomatology is vague and often goes unnoticed adnexal tumor a little intense discomfort that often confuse the ill and the same optional with gastrointestinal situations and character falsely originated in the urinary tract. When ovary malignancy is manifested, 79% of cases are diagnosed in advanced stages, symptoms up to affected or invaded organ. At that time, woman says intense digestive symptoms with pelvic or low abdominal pain, constipation and periodic diarrheas, digestive disorders; in addition, transvaginal bleeding. Commonly sick are treated thinking about ulcerative origin, colitis and not rare phenomena of hepatic pathology, mainly from the gallbladder. The abdominal diameter and volume increases abruptly by ascites and this encourage the emergence of progressive dyspnea, according to the number of liters that make upward pressure on diaphragms preventing respiratory movements. Unlike other neoplasms, sick ones increase their body weight by malignant fluid in the abdominal cavity. When a tumor of ovary is diagnosed accidentally in the initial form, usually make the diagnosis of benign adnexal tumor, it is generally functional in the majority of cases of fertile women. This regresses to the next period menstrual or improve painful symptomatology; the diagnosis of the malignant neoplasm of ovary, is also accidentally or incidental to a gynecological examination and sometimes by presence of torsion of the pedicle of the ovary, it is necessary to perform a laparotomy exploratory by presence of acute abdomen, most of the time without oncology-surgery criterion. Once diagnosed as a malignant ovarian tumor, survival prognosis is related to the following factors:

- Age and menopausal status
- Tumor size
- Tumor stage
- Features of neoplasm (US, CT, MRI) imaging
- Presence or absence of symptoms
- Values of the tumor marker (CA-125, CA 19.9)
- Compared with the bilateral, unilateral.

Never should be overlooked in addition to adnexal tumor-targeting anamnesis, physical examination with recto-vaginal, touch key to expand the possibilities of initial surgery obviously made by an oncologist.Initial assessment of patients with suspected ovary cancer after the anamnesis initial, physical examination, laboratory tests and, tumor marker CA-125, should be directed the study to research content in the abdominal cavity. Therefore nor imaging studies such as Sonography, CT, MRI and special techniques of tracking with radioactive isotopes should miss; none of these give to detail the correct staging of neoplasia, at the end of the study should be performed a CT scan of abdomen, chest x-ray and a bone scan. When technically possible, the preferred US is the performed vaginally with Doppler color, as 1st choice, for suspected adnexal tumor alone, with one sensitivity higher than the 93.5% and a specificity of the 91.5%; If it is not possible to do MRI is the most appropriate study, especially if there is suspicion of tumor activity outside the pelvis, with a sensitivity of the 91.1% and a specificity of 84%; the CT showed sensitivity of the 87.2% and specificity of 84% [25]. Neoplastic Antigen in serum CA-125, may be elevated in other malignant neoplasms as: breast, pancreas, colon cancers; bronchogenic and endometrial cancers too. Therefore, it is not recommended as a single modality nor standard to make diagnosis of ovary neoplasm, when result is high, obtained 3 times its value, it's considered with a sensitivity of the 78.7% and a specificity of the 77.9%. The CA-125 can be found high in the different benign ovary pathologies, mostly pre-menopausal with pathology related to infertility such as endometriosis, pelvic inflammatory disease, endometriosic cyst, hepatitis, pregnancy, menstruation peritonitis and recent abdominal surgery. Unless this evaluation shows evidence of disease outside the abdominal cavity, laparotomy exploratory-legalized, is an essential part of the initial assessment of the patient. Romagnolo, Park and Desfeux showed not find significant difference in patient'ssurvival with ovarian cancer in early stages or in neighboring tumors of the ovary [26-28]. Fertility-sparing surgery is recommended in most adnexal located in an ovary, as neighboring tumors, or low malignant potential, having stage I insurgical pathological ovary cancer.Without altering the above survival of the patient.

Histo-Pathological and Molecular Diagnosis

The strains of ovarian cancer, are caused (most common) epithelial, germ cell and gonadal stromal. The first derived adenocarcinomas serous, mucinous, endometrioid, undifferentiated, clear, small cell and Brenner tumor cells. Those groups constitute 45% of malignant neoplasms. 5% of endometrioid tumors arise in foci of endometriosis from 25% to 33% of cases are associated with endometrial cancer. Clear cell have the worst prognosis of survival. The epithelial feature raise non-specific tumor markers, in a significant way the CA-125 in the mucinous and non-mucinous tumors, rises with greater frequency CA -12.4, with a formidable response from both schemes with chemotherapy involving derivative platinics treatments.

Non-epithelial, mainly the germs, manifested most often in young people, who are menstruating, mainly elevated tumor markers: carcino-embryonic Ag. Alpha-fetoprotein, and chorionic gonadotropin Beta fraction; Cell tumors germ of the ovary account for 20% of neoplasms and only 3% is associated with malignancy. Tumors are a complex and heterogeneous group of neoplasms, and so far there aren't defined Etiologic factors that are associated with your presentation, even though different chromosomal alterations (3q27-q28 12q22, 5q34q35, chromosome 14) have been described and processes related to DNA repair (short arm of chromosome 12) that contribute to its development. Gonadal digenesis is associated with the growth of disgerminoms up to

50% of cases and some patients showed that overexpression of the gene p53 [29] exists. The most aggressive of these, is germinal endodermic ovarian cancer, with a surprising elevation of Alpha-fetoprotein and Beta fraction, malignancy with poor prognosis. Dysgerminom, being the most frequent of all germinal, hasn't tumor marker, but it tends to raise significantly the lactic dehydrogenase. Currently intends to classify malignancies of the ovary according to its morphological and molecular, structure and grouping the different varieties in type I and type II (Table 1).

In papillary serous carcinomas, its proposes to classify them into high and low grade (Tables 2 and 3), using the method proposed by MD Anderson, is based on number of mitoses and the nuclear pleomorphism [30].

- **Low grade:** Mild-to-moderate pleomorphism<12 mitosis per 10 fields 400 x
- **High grade:** Pleomorphism marked with more than 12 mitoses per 10 fields 400 x

By the time, there aren't molecular markers that identify groups associated with prognosis. Among the factors related are: heterogeneity tumor, size of the studied population and the different techniques of processing samples [6].

Comment

Ovary cancer will remain its natural history a scourge for high-risk women, as his diagnosis in early stages is given in a very low percentage, therefore the majority of patients will die despite the known treatment today. By the time, there isn't a low-cost effective method to carry out proper screening. I deem it necessary to make every woman from menarche a pelvic US as a research study and those with ovarian tumor; they must have the panel of tumor markers for diagnosis. Because they have to remember that, ovarian cancer is curable only in stage I and good prognostic factors founded in the Natural history ovary cancer.

Conclusions

- Ovary cancer hasn`t an efficient research methods.
- There are early diagnosing tools, knowing the high risk factors, to use abdominal or better vaginal US, as image *sinequanon* study and Immunohistochemistry studies.

TYPE I	TYPE 2
Serous papillary, low-grade	Serous papillary, high-grade
Endometrioid, grade I and II	Endometrioid grade III
Mucinous Tumors	Undifferentiated carcinomas and Mixed Müllerian tumors.

Table 1: Classification of ovarian tumors based on genetic mutations and biological behavior.

Grade	KRAS/BRAF	TP53	Age of presentation	Response to Platinum
Under	Mutant	Native	Approx. 43 years	Resistant
High	Native	Mutant	Approx. 63 years	Sensitive

Table 2: Comparison between low-high grade tumors.

Clinical stage	Distribution (%)	Survival at 5 years (%)
I	20	90
II	10-15	80
III	45	20-30
IV	15	< 5

Table 3: Frequency and survival at 5 years in relation to clinical stage.

- The natural history of the Ca ovary tells us that it will continue today and for several decades, as the tumor that more lives copper in women of productive age.

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