Hormonal Imbalance and Ovarian Cancer

(A review article)

Saudi Arabia, Medina, Taibah University- Collage of Medicne
Aghareed. M. Aljohani

Abstrac

Ovarian cancer is an aggressive neoplasm involving variety of risk factors such as hormonal imbalance and it is the seventh most common cancer among women world widely. The aim of this article is to summarize the types, the incidence, possible risk factors and pathophysiology of ovarian cancer. Also, causes of sexual hormonal imbalance and the impact of hormonal imbalance in the case of ovarian cancer. There are many studies reported that hormones imbalance as a risk factor which have a significant role in the pathogeneses of ovarian cancer. Factors related to increase estrogen level such as HRT (Hormonal replacement therapy) and menopause considered as risk factors. In contrast, factor related to reduce estrogen exposure such as OCP (Oral contraceptive pill) and pregnancy act as protective factors. Other factors such as gene mutation, smoking and obesity have a role in ovarian cancer. A lot of studies and researches conclude that there is a relation between ovarian cancer and hormonal imbalance as high level of estrogen induce ovarian cancer and progesterone is acting as a protective factor.

Index Terms: Ovarian cancer, risk factors, hormonal imbalance, estrogen, progesterone, contraceptive pills.

INTRODUCTION

Ovaries are female glands found in the reproductive system. In 2012 ovarian cancer is consider the seventh most common cancer among women world widely. Furthermore, in Saudi Arabia there were 194 cases of ovarian cancer among females accounting for 3.0% of all newly diagnosed 6,364 cases among females in year 2013 [1,2].

Particularly, sexual hormonal balance is an important factor to protect the ovaries. Hormonal imbalance can lead to several pathological problems, which may be caused by improper diet, stressful or depressed lifestyles and use of drugs that may be leads to hormonal imbalance. Epidemiological data suggest that endogenous and exogenous sex hormones may play important roles in the pathogenesis of the ovarian cancer. Although based on limited data, there is current observed tendency evidence suggests possible etiologic roles for elevated androgens, estrogens and decreased progesterone in the pathogenesis of ovarian cancer [3, 4, 5].

The aim of this study is to summarize the types, the incidence, possible risk factors and pathophysiology of ovarian cancer. This study also assesses the causes of sexual hormonal imbalance, and finally to detect the impact of hormonal imbalance in the case of ovarian cancer.

1.1 Ovarian cancer

Cancer is a cruel disease among which cells of the body grow over control. Cancer is always named according to the part of the body where it starts, even if it spreads to further body organs later on. If cancer starts in the ovaries, it will be called ovarian cancer. One on each side of the uterus, female have ovaries that are located in the pelvic cavity, which produce eggs and make female hormones. Ovarian carcinomas are a heterogeneous group of neoplasms commonly divided based on degree of differentiation, appearance and type [6].

1.2 Types

Ovarian cancer is divided into epithelial surface tumor, germ cell tumor, sex cord-stromal tumor, miscellaneous tumor and metastatic tumor. Another pathological classification is primary and secondary. Primary, which means the cancer cells arise from the ovary itself, where secondary, is resulting from spreading of other cancer such as breast, stomach or gallbladder cancer. Furthermore, primary ovarian cancer divided into epithelial origin and non-epithelial origin. Epithelial ovarian cancer is the most common type. According to molecular and histopathology alterations of genes, ovarian carcinomas can be divided to 70% of high-grade serous, 10% of endometrioid, 10% of clear cell, 3% of mucinous and lastly low- less than 5% of grade serous carcinomas. The five tumor types are morphologically diverse and resemble carcinomas of the uterus. Lastly, non- epithelial origin include germ cells and stromal cells [7, 8].

1.3 The incidence

In the worldwide, ovarian cancer is the seventh almost common cancer among female in 2012. Furthermore, between January 01 and December 31, 2013 in Saudi Arabia, the whole quantities of cancer incident cases mentioned according to the Saudi Cancer Registry (SCR) were 15,653. Overall most cancers used to be higher among females than males; it affected 11,645 (77.6%) of Saudis and 3,356 (22.3%) of Non-Saudis. Among Saudis 5,281 (45.3%) were male and 6,364 (54.7%) were female. Moreover, there were 194 cases of ovarian cancer among females accounting for 3.0% of all newly diagnosed cases among females (6,364) in year 2013.This cancer ranked seventh among women population [1,2].

1.4 The risk factors

There are many risk factors of ovarian cancer and the most

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common of them are including genetic abnormalities such as having a family history of ovarian cancer or genetic mutations on breast cancer gene 1 (BRCA1) and breast cancer gene 2 (BRCA2) or Lynch syndrome [9]. Previous condition of breast, colorectal or endometrial cancer can lead to ovarian cancer. The age is considering as risk factors. Women aging 55 years or older may develop ovarian cancer due to hormonal changes, in addition to the time of starting and ending menstrual cycle. Women whosoever have delivered at least one child, particularly before age 30, are at a lower chance for developing the disease. There is higher incidence of ovarian cancer in unmarried females and married females with low or no parity. Women who breastfeed further decrease theirs risk. Another factor that increases the risk of developing ovarian cancer is using hormonal replacement therapy. Moreover, Obese Women with a body mass index (BMI) about 30 or larger might also have a higher gamble of growing ovarian cancer [10, 11, 12, 13].

Finally, smoking leads to increase the risk of borderline and invasive mucinous ovarian tumors. Furthermore, a lowered risk on endometrioid and clear cell ovarian tumors used to be observed, while no companionship might have been found to serous ovarian tumors [14].

1.5 Pathophysiology

The molecular profile of various kinds of ovarian cancer is characterized by mutation in different genes which include; TP53, ERBB2, BRAF, CTNNB1, PTEN, PIK3CA, ARID1A, PPP2R1A, BCL2 and KRAS.TP53 mutations are represent AL mostly in 96% of high-grade serous ovarian carcinomas. The ovaries have three types of cells; each one can be differentiated into tumor cells. Germ cell tumors start from the cells that produce the eggs (ova). Stromal tumors start from structural tissue cells that hold the ovary together and produce the female hormones estrogen and progesterone. Finally, (the most common type) which is epithelial tumors that begin from the cells that cover the outer surface of the ovaries [15].

There are two main groups of ovarian tumors. Type I (borderline tumors) is slowly growing tumor and develop from well-established precursor lesions. Type I which included; (endometrioid, low-grade micropapillary serous carcinoma, mucinous, and clear cell carcinomas), they are stable tumors genetically and they are characterized by mutations in many genes including KRAS, BRAF, PTEN, and moreover beta-catenin. Type II tumors are growing rapidly, and it is highly aggressive neoplasms. Most cases of ovarian cancer belong to Type II, which include (high-grade serous carcinoma, malignant mixed mesodermal tumors and undifferentiated carcinomas). Type II tumors are characterized by high level of genetic instability and mutation of TP53 [15,16].

The morphologic and molecular genetic data that lead to development of the major types of epithelial ovarian cancer is supported by different pathways. Benign serous tumor is a spherical masse contains serous fluid; small masses are generally unilocular while the larger serous cysts are multiloculated [16]. Malignant serous tumor may have solid areas in the cystic mass. Mucinous tumor are much larger than serous tumor. They are smooth-surfaced cysts with characteristic multilocu-

lations containing thick and viscid gelatinous fluid. Benign tumors generally have thin wall, but malignant varieties usually have thickened areas. The endometrioid adenocarcinoma is distinguished from serous and mucinous carcinomas by typical glandular pattern. There are no clearly defined criteria for borderline endometrioid tumors, but are usually large, unilateral, partly solid and cystic. Clear cell or mesonephroid tumor is characterized by tubules, glands, papillae, cysts and solid sheets of tumor cells like cells of renal adenocarcinoma [16,17].

Low- and high-grade serous carcinoma most probably arise via different pathways, the former progressing along an adenoma–borderline tumor–carcinoma sequence involving mutations in KRAS and BRAF. Mucinous carcinomas arise via an adenoma-borderline tumor-carcinoma sequence with mutations in KRAS. Endometrioid carcinomas arise from endometriosis with mutations of CTNNB1 (the gene encoding beta-catenin) and PTEN. The genetic alterations of clear cell carcinoma are supporting an origin from endometriosis, but they are the least investigated tumor [16,17].

2.1 Sex hormones

Sex hormones are steroidal hormones such as estrogen, progesterone or testosterone which is produced particularly by the testes, ovaries or adrenal cortex. Under control of two other sex hormones from the anterior pituitary gland, have a magnificent mechanism. They have many effects on the function and growth of the reproductive organs and the development of secondary sex characterization [18].

2.2 Female Sex hormones

2.2.1 Estrogen

It is a type of steroidal hormones, which is secreted in small quantity in childhood. During puberty, the secretion increases sharply resulting in changes in the sexual organs. Estrogen is responsible for the maintenance and development of female sexual characteristics. Estrogens cause marked proliferation of the endometrial stroma and significantly increased the development of the endometrial glands, which will later help in providing nutrition to the implanted ovum. In addition, it has many effective roles, for example, protection against metabolic syndrome because estrogen deficiency can lead to this syndrome and prevention of bone loss as it acts on osteoclasts and osteoblasts to reduce resorption of bone [18,19].

Its synthesis occurs in the theca cells and granulosa of the ovaries and in the corpus luteum. Moreover, fat cells and bones can produce estrogens. Fat cells increase serum estrogens by converting androgen to estrone. Also, bones convert testosterone to estrogen in the sake to help the epiphyses maturation [18,19].

Estrogen in plasma is present in three different forms, which are β-estradiol, Estrone and Estriol. These different forms of estrogen are synthesized from the cholesterol or acetate. There are two types of estrogen receptors located on nuclear membrane of target cells which are α and β estrogen receptors. The α-estrogen receptors are found in heart, kidneys

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and liver. The β estrogen receptors are present in different tissues such as ovaries [18,19].

2.2.2 Progesterone

is another steroidal hormone, it is secreted in a small amount in non-pregnant woman by theca interna cells of the ovaries during the first half of menstrual cycle, but a large amount of progesterone is secreted in the latter half of each menstrual cycle. A small quantity of progesterone is secreted from adrenal cortex. The major function of progesterone is preparation of the uterus for pregnancy and the breasts for lactation. Another important effect of progesterone is its ability to antagonize estrogen by decreasing the expression of estrogen receptors, as progesterone inhibits estrogen-mediated endometrial proliferation [18, 19].

It synthesizes by the placenta during pregnancy and from pregnenolone by the action of 3β-HSD in corpus luteum. Also, it synthesizes as well as by adrenals, as a step in androgen and mineralocorticoid synthesis. The progesterone receptors located on the nuclear membrane of target cells are A-progesterone receptors and B-progesterone receptors. Each type of progesterone receptor's site is not clear. As estrogen, progesterone acts through genes too [18,19].

3.1 Hormonal imbalance

Hormones play a major role in the development of human females (especially female genital organs) and hormonal imbalance may be caused by several pathological factors (as improper diet, stressful lifestyles and improper use of drugs) all can lead to hormonal imbalance.

Many researches have shown that normal ovarian growth and development are dependent on the proper hormonal balance. Hormonal regulation is more complicated in females than in males because of the variety effects of feedback on different hormones, for example during the stages of menstrual cycle and pregnancy. A disturbance in the developing of the ovary may occur due to changes in the hormonal environment. Thus, this disturbance can lead to many ovarian abnormalities which included ovarian cancer [3,18,19].

3.2 Causes of sexual hormonal imbalance

Hormones play a significant role in the pathogeneses of ovarian cancer. Endocrine disruptors interfere with the production, metabolism, and action of natural hormones in the body. Disrupt hormones needed for homeostasis and developmental processes and Alter estrogen, androgen, thyroid, neuroendocrine and metabolic signaling. Therefore, the passable mechanism of endocrine disruptors may involve some herbicides (atrazine), dichlorodiphenyldichloroethylene (DDE) and pesticides dichlorodiphenyltrichloroethane (DDT). In addition, dioxin which is an example of Persistent Organic Pollutants (POPs). Drugs such as Hormonal replacement therapy (HRT) and contraceptives, stress and improper diet can lead to hormonal imbalance. Random and a cross-sectional study were used to collect data from young females aged between 15-40 years, in Karachi and Pakistan. The study concluded hormonal imbalance has relation with use of drugs, food intakes and other factors like workloads and depression [20, 21].

3.2.1 Contraceptives

They are consisting of female sex hormones (estrogen and progesterone or progesterone only) and they used to regulate pregnancy by changing the normal balance of hormones to prevent ovulation. Oral contraceptive pill (OCP) use is associated with a substantial protective effect for ovarian cancer [20, 21].

3.2.2 Hormonal replacement therapy

There are many studies conclude that risk of ovarian cancer is greater in users of estrogen-only HRT than in combination of estrogen-progestin HRT users. Using estrogen-only replacement therapy for female, particularly for ten years or more than that, lead to increase the risk of developing ovarian cancer. So, Women who are using short period of estrogen-progestin-only replacement therapy are not at high risk. So, the combination of estrogen and progesterone is considered more advantageous because progesterone prevents the estrogen-induced cancer and hyperplasia of myometrium [22].

3.3 Impact of hormonal imbalance in the ovarian cancer

3.3.1 Estrogens

Estrogens are an important etiologic risk factor that associated with endometrium carcinoma and in many studies; the adverse effect of HRT use was greater for clear cell and endometrioid tumors. Ovarian development depends on estrogenic pathways, thus, withdrawal or exposure to estrogen and estrogen-like substances may affect the proper function. Aromatase, estrone (E1) sulfatase and E1 sulfotransferase activities were examined in endometrium and endometrial cancer tissue preparations. Aromatase and E1 sulfatase activities in endometrial cancer tissues were found to be significantly greater than in normal endometrial tissues. However, the activity of E1 sulfotransferase did not show any difference between benign and malignant tissues. high production of estradiol, involving greater expression of aromatase and deficiency of 17h-hydroxysteroid dehydrogenase type 2 (that converts estradiol to estrone) have been shown in endometriotic lesions . Moreover, after menopause there is a possible etiologic role of ovarian estrogens in development of clear cell tumors and endometrioid. [22, 23].

Finally, some environmental exposure to natural estrogen may affect the ovarian development process. Some animal models show failure of normal follicle development when exposed to estrogenic endocrine disrupting. One of them is laboratory mice were used to demonstrate that exposure to estrogenic compounds cause a failure in normal ovarian follicle formation [22, 23,24].

3.3.2 Progesterone

Progesterone might protect against ovarian tumor development. The high ovarian production and blood levels of progesterone during pregnancy, such protective effect of progesterone could account for a beneficial effect. Many studies showed that progesterone has a potent apoptotic effect on ovarian epithelium, which could be mediated by transforming growth factor-h and up-regulation of p53 expression. Progestin induces differential regu-

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lation in the ovarian epithelium of TGF-beta, a change in the expression of which is highly associated with apoptosis. Previous data suggest a possible biologic mechanism for the protective association between progesterone and reduced ovarian cancer risk. In summary, evidence is suggesting that progesterone level has potent effects such as controlling apoptosis pathway for cancer prevention, which in turn reduce the risk of ovarian cancer [24,25].

Discussion

Evidence that suggesting, the role concerning estrogens in ovarian tumors is conflicting. Long-term use of any type of HRT leads to increase the risk of growing cancer and focuses on the etiologic importance of persistently raised estrogen concentrations. Some studies observed that the impact of estrogen and progestin combination is weaker than estrogen-only formulations due to the role of the progestin nature. Therefore, progesterone level has potent effects such as controlling apoptosis pathway for cancer prevention, which in turn decrease the risk of ovarian cancer [25].

Provided the long latency of ovarian carcinoma and that among some researches the impact of HRT on risk was confined to users help the role of estrogens as a stimulator of the growth of preexisting, undiagnosed tumors. 329 women who suffering from ovarian cancer have been identified by Lacey and colleagues during the follow-up, results show when considering adjusted type of menopause, age and use of oral contraceptives, that the use of estrogen only was significantly associated with ovarian cancer. The study found that women who used estrogen-only replacement therapy, especially for 10 years or more , were at significantly high risk of ovarian cancer (P value <.001). On the other hand, women who used short period of estrogen and progestin replacement therapy were not at high risk [25, 26].

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Conclusion

Hormones have a significant role in the pathogeneses of ovarian cancer. Excessive estrogen exposure is a key risk factor for gynecologic malignancies and benign proliferative disorders [3]. Risk factors such as HRT, menopause, genes mutation and obesity are associated with increased estrogens circulating levels. However, obesity have a relatively weak adverse effect on increasing risk, females, who are using estrogen-only replacement therapy, especially for ten years or more than that, are at high risk of developing ovarian cancer. Moreover, pregnancy has a beneficial effects against ovarian cancer that during pregnancy progesterone levels increased and suppression of ovulation. In addition, Oral contraceptive with high-progestin potency decreases the risk of ovarian cancer, so progesterone play a significant role as a protective factor against ovarian cancer, such as controlling apoptosis pathway for cancer prevention [27, 28, 29].

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