OVARIAN CANCER IN YOUNG WOMEN: A COMPREHENSIVE ANALYSIS OF CLINICAL FEATURES, DIAGNOSTIC CHALLENGES AND THERAPEUTIC OPTIONS TO IMPROVE MANAGEMENT AND QUALITY OF LIFE

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Abstract: Objective: To conduct a comprehensive investigation and synthesize the distinct clinical features of ovarian cancer in young women, identifying challenges in diagnosis and evaluating treatment options. Methods: A narrative bibliographic review was conducted using the PubMed database, resulting in 1,197 initial articles. After rigorous application of the inclusion and exclusion criteria, only 16 articles were selected as official sources for the study. Results: Early diagnosis of ovarian cancer, especially in young women, presents significant challenges, with only 19% of cases detected early. Methods such as transvaginal ultrasound (TV-USG) and serum markers, including CA-125 and HE4, play a crucial role in diagnosis. Genetic mutations, such as BRCA1 and BRCA2, guide genetic counseling. Treatment is highly variable, highlighting the multidisciplinary approach. Conclusion: The review focuses on ovarian cancer in young women, highlighting challenges in early diagnosis arising from histological variety and the absence of initial symptoms.

Keywords: Ovarian cancer; Young women; Diagnosis.

INTRODUCTION

Ovarian cancer (OC) assumes significant relevance in global public health, ranking as the seventh most common malignancy worldwide. It is often characterized by a late diagnosis, carrying an unfavorable prognosis, being considered the most lethal gynecological cancer (ZHANG Y. et al., 2019).

OC encompasses a histological variety, with germ cell tumors being subdivided into dysgerminoma, immature teratoma, endodermal sinus tumor, choriocarcinoma, polyembryoma, and malignant mixed ovarian germ cell tumors (MOGCTs). Epithelial cell tumors are segmented into subtypes such as high-grade serous, endometrial, clear cell,

mucinous and low-grade (DELLINO M. et al., 2020).

The analysis of risk factors for OC points to changes in lifestyle, associating smoking, Westernized diets, obesity and a lower number of pregnancies with an increased risk. On the other hand, increasing parity and the use of oral contraceptives present protective measures against this neoplasm (ZHANG Y. et al., 2019).

The diagnosis of OC often occurs in advanced stages, which challenges treatment options and results in reduced survival rates (ZHANG Y. et al., 2019). Furthermore, most clinical trials on the diagnosis and treatment of OC have focused on postmenopausal women (LEWIS D. R. et al., 2021), highlighting the difficulties in finding effective diagnostic techniques for early detection.

The diagnosis is based on the use of a tumor marker, the CA-125 protein, combined with imaging tests (LEWIS D. R. et al., 2021). An increase in the incidence of OC was also observed in women carrying the MLH1 and MLH2 mutations, with a previous diagnosis of Lynch syndrome, the majority of these cases diagnosed before the age of 50.

It is recognized that early diagnosis of OC and improvements in treatment result in higher survival rates, but these survivors may experience symptoms such as fatigue, anxiety, depression, sexual dysfunction, physical changes, and financial difficulties. In many cases, OC affects women of working age, resulting in possible financial complications due to time off and psychological challenges resulting from a cancer diagnosis. Thus, returning to work emerges as a source of emotional and financial support, contributing to improving the health-related quality of life of women CO survivors (MAMGUEM KAMGA A. et al., 2019).

The purpose of this review is to investigate and summarize the specific clinical features of ovarian cancer in young women, address challenges related to diagnosis, and evaluate available treatment options. The objective is to offer relevant information to improve the management of this condition, with an emphasis on early detection, effective therapeutic interventions and improving patients' quality of life.

METHODOLOGY

This study consists of an integrative review that was developed in accordance with the PVO strategy, which covers the analysis of the Population or Research Problem, the Variables considered and the Outcomes evaluated. The research was conducted based on the central question that guided the investigation: "What are the distinct clinical characteristics of ovarian cancer in young women, what specific challenges are associated with its diagnosis and what are the most effective treatment options for this population group?". Based on the aforementioned criteria, the population or problem of this research refers to young patients diagnosed with ovarian cancer, focusing on identifying the clinical characteristics that distinguish them, as well as analyzing the specific challenges related to the diagnosis of this age group. Additionally, the research aims to evaluate the most effective treatment options for this demographic.

The search was conducted in the PubMed Central (PMC) database and involved the combination of descriptors, together with the Boolean operator "AND". The initial search identified a total of 1,197 articles which were then subjected to rigorous selection criteria. The inclusion criteria stipulated: articles written in English; published between 2018 and 2023; articles that addressed the themes relevant to the research, including review studies and meta-analyses and available in full. On the other hand, the exclusion criteria comprised articles that did not directly

address the central theme of the research and that did not satisfy the other inclusion criteria. After rigorously applying these criteria, a total of 16 articles were selected from the PubMed database to compose the present study. These articles will provide valuable information about the clinical features of ovarian cancer in young women, challenges related to diagnosis, and effective treatment options for this population group.

DISCUSSION

Early diagnosis of ovarian cancer in young women represents a significant challenge, often discussed in the search for practices that facilitate detection. According to DIJMĂRESCU A. L. et al. (2019), only 19% of malignant ovarian tumors are diagnosed in localized stages, with the difficulty attributed mainly to their silent and asymptomatic nature, often resulting in accidental discoveries. The definitive diagnosis of ovarian cancer is obtained through histopathological analysis, making the identification of methods independent of the surgical approach a challenge to be overcome.

Although transvaginal ultrasound (TV-USG) is still common to detect ovarian masses, its non-specificity often requires complementation with computed tomography or magnetic resonance imaging of the abdomen and pelvis, as highlighted by SESSA C. et al. (2020). Features suggestive of malignancy on ultrasound include a solid mass, mixed echogenicity, irregularity, multilocularity with a diameter ≥ 100 mm, intense vascularization and association with ascites (SESSA C. et al., 2020) (DIJMĂRESCU A. L. et al., 2019). Given its non-specificity, non-invasive diagnostic complementation must include the measurement of serum markers, with DIJMĂRESCU A. L. et al. (2019) highlighting the diagnostic sensitivity of human epididymal protein 4 (HE4), in

conjunction with increased dosage of CA-125. The ROMA index (Risk of Ovarian Malignancy Algorithm) is highlighted as a highly accurate method for detecting malignant ovarian pathologies, especially in pre-menopausal women, where an index ≥ 12.5% indicates an increased risk of ovarian cancer. Sessa C. et al. (2020) describe other serum markers, such as alpha-fetoprotein, beta HCG, inhibin B and anti-Mullerian hormone, which can be considered in the diagnosis and management of non-epithelial ovarian cancers.

Elezaby M. et al. (2019) report that 15% of all ovarian cancers are associated with genetic mutations, highlighting BRCA1, with an estimated risk of 54%, and BRCA2, with a risk of 21%. This knowledge guides genetic counseling as part of ovarian cancer screening, especially when there is a positive family history. Guidelines from the European Society of Gynecological Oncology (ESGO) and European Society of Pediatric Oncology (SIOPE) describe the relevance of genetic counseling in specific cases, such as bilateral germ cell tumors, unilateral germ cell tumors with gonadal or pubertal delay, Sertoli-Leydig and hypercalcemic small cell ovarian carcinomas - neoplasms often associated with known genetic alterations and familial tumor syndromes, allowing early screening (SESSA C. et al., 2020). In cases of positive genetic tests, the American College of Gynecologists and Obstetricians and the National Comprehensive Cancer Network recommend prophylactic bilateral salpingo-oophorectomy for women without the desire to become pregnant or over 35 years of age. For those outside this profile, regular screening with USG-TV and CA-125 dosage is the recommendation (ELEZABY M. et al., 2019).

CA-125, HE4 and the ROMA index emerge as valuable tools for the preoperative assessment and diagnosis of ovarian cancer (DIJMARESCU A.L. et al., 2019). CA-125

and HE4, in particular, are diagnostic criteria due to their high sensitivity and specificity, and can complement ROMA. However, the effectiveness of these markers highlights the complexity of diagnosis at early stages.

Studies, such as those by PAMPININI V. et al. (2019), reveal gaps in understanding the effects of chemotherapy on the quality of ovarian tissue in young patients with ovarian neoplasia. Follicular activation resulting from chemotherapy, potentially leading to atretic death of primordial follicles, is suggested as a dominant mechanism in ovarian failure.

JAMMAL M.P. et al. (2020) emphasize the importance of new biomarkers for diagnosis and prognosis. Markers related to the inflammatory response, such as leukocyte count and NLR and PLR ratios, emerge as prognostic factors. Furthermore, the study indicates the association of increased glucose levels with carcinogenic development. The analysis by CARTER N.J. et al. (2018) highlights the identification of pathogenic variants in genes associated with the hereditary risk of ovarian cancer. These tests, applied to a broad cohort, provide crucial information for medical management and genetic counseling, regardless of histological subtype or age at diagnosis.

TREATMENT

The European Society of Gynecological Oncology (ESGO) and European Society of Pediatric Oncology (SIOPE) guidelines provide evidence-based guidance for the treatment of non-epithelial ovarian cancer in adolescents and young adults. The systematic review, covering studies from 1998 to 2018, highlights the need for a multidisciplinary approach, accurate diagnosis and risk stratification. Treatment varies depending on the stage of the disease, recommending aggressive surgery followed by adjuvant chemotherapy for early stages and removal of peritoneal disease followed by chemotherapy for advanced stages. In refractory cases, participation in clinical trials is emphasized, adapting to advances in tumor biology (SESSA C. et al., 2020).

In addition to treatment, a study in Japan explored the impact of age on the clinicopathological characteristics and survival of patients with ovarian epithelial neoplasms of reproductive age. The results highlighted statistically significant differences in survival between patients aged 31-40 years and ≤30 years, highlighting age as a relevant prognostic factor, in addition to clinicopathological differences stratified by age (HANATANI M. et al., 2020).

Moss J.L. et al. (2019) investigated the relationship between social determinants of health and health-related quality of life (HRQOL) in women with ovarian cancer. Surprisingly, no differences in HRQoL were observed related to race, age, clinical characteristics, or distance to access treatment. However, a significant association between type of health insurance and HRQoL was identified, indicating better scores for women with private insurance compared to those without private insurance. The analysis revealed a gradient association, highlighting the crucial role of healthcare access in HRQoL disparities following ovarian cancer treatment.

Malignant ovarian germ cell tumors (TGMO) encompass distinct categories, being TGMO and TGMND, presenting histologies such as dysgerminoma, yolk sac tumor, choriocarcinoma, embryonal carcinoma and immature teratoma, as well as mixed germinal tumors. Over time, surgical procedures have become less invasive, contributing to improvements in patient survival rates (GHADDAB I. et al., 2020).

According to data from the American Cancer Society, the overall survival rate and therapeutic efficacy are directly related to

the pathological subtype and the moment of discovery. Treatment readiness positively impacts prognosis. Despite this, a significant portion of women undergoing treatment face infertility challenges, reporting an incidence of 5% to 10% (GHADDAB I. et al., 2020).

According to PyeonI S. Y. et al. (2020), in recurrent ovarian cancer, a palliative approach, including chemotherapy, is considered due to the complexity of the treatment. Despite the aggressiveness of this procedure, some patients choose not to continue with chemotherapy. Notably, home care has been shown to be more likely to have favorable outcomes in terms of death outcomes.

Studies highlight the heterogeneity of malignant ovarian germ cell tumors, highlighting the importance of a less invasive surgical approach. Furthermore, the relationship between therapeutic efficacy and time of diagnosis highlights the need for rapid interventions. The issue of post-treatment infertility and the consideration of palliative approaches in ovarian cancer recurrence contribute to a comprehensive view in the management of this complex condition.

According to Swisher, E.M. et al. (2022), the combination of chemotherapy with Veliparib presents therapeutic benefits and antitumor activity in patients with ovarian carcinoma. The Velia study, involving 1440 patients, explored the addition of Veliparib to first-line chemotherapy, demonstrating the effectiveness of this combination in the treatment of ovarian cancer.

Other studies, such as that by Liu, L.Y. et al. (2020), analyzed women with recurrent ovarian cancer recently treated with immune checkpoint inhibitors (ICI). These agents have shown a positive impact on concomitant or subsequent chemotherapy. However, there is a need for additional studies to explore optimal combinations of chemotherapy and ICI.

A cross-sectional study of childhood cancer survivors, conducted by George, A.S. et al. (2019), revealed late effects, including premature ovarian failure (POI) in women between 13 and 21.9 years old. POI, characterized by irregular menstruation and menopausal FSH levels before the age of 40, is associated with several complications, highlighting the importance of future research to better understand these impacts and develop management strategies.

The studies address different therapeutic approaches for ovarian cancer. While the combination of veliparib with chemotherapy stands out as an effective option, ICIs also demonstrate benefits, especially in patients with platinum-resistant disease. The detection of late effects, such as POI, highlights the importance of long-term monitoring and fertility preservation strategies. This evidence reinforces the need for more research to improve the implementation of these treatments as supporting pillars in the management of ovarian cancer, aiming to improve patients' survival and quality of life.

FINAL CONSIDERATIONS

Given the histological diversity of this cancer, early diagnosis represents a significant difficulty, often occurring late or incidentally. This delay may be attributed to a lack of understanding of the natural history of the disease or the absence of lesions and symptoms in the early stages. For diagnosis, biomarkers such as CA-125 and HE-4, possible alternatives or additions to the ROMA index, play a crucial role. The continuous search for new biomarkers is essential to improve diagnostic accuracy. Adequate treatment is of critical importance, with the survival rate and therapeutic efficacy directly correlated to the specific type of cancer and the moment of its detection. The urgency of starting treatment is highlighted, as early diagnosis favors a more favorable prognosis. Therapeutic strategies

vary depending on the stage of the disease: in early stages, the recommendation is an aggressive surgical approach followed by adjuvant chemotherapy, while in advanced stages, peritoneal removal precedes the administration of chemotherapy.

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