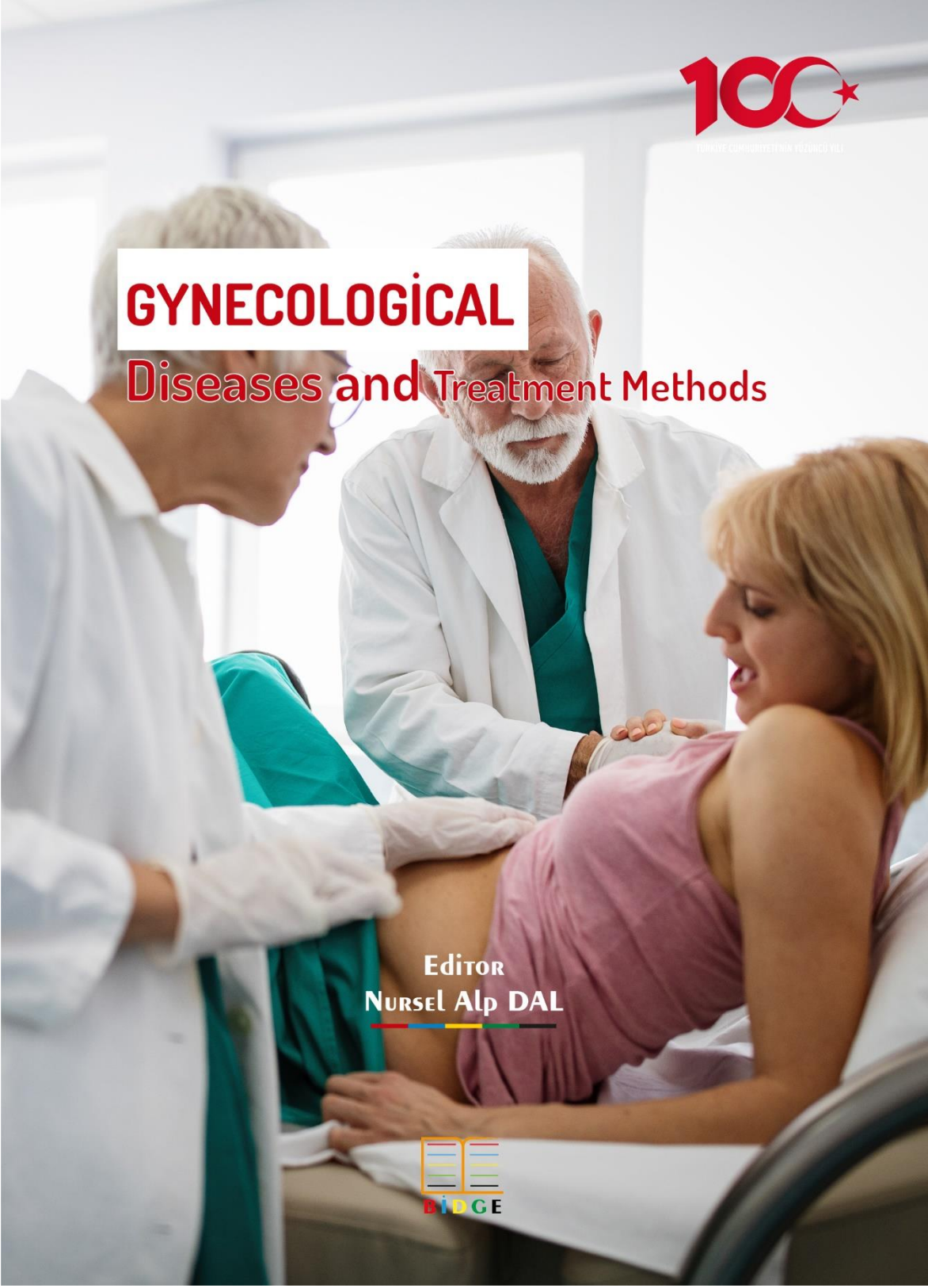
GYNECOLOGİCAL
Diseases and Treatment Methods



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PREFACE

Considering their biological characteristics, women have the potential to experience more problems with their health at different periods of their lives. In some gynecological diseases, early diagnosis and treatment methods can be lifesaving. In this context, our book is a study that will contribute to both health professionals and everyone who is interested in the subject.

In our book titled “Gynecological Diseases and Treatment Methods”, among the frequently encountered gynecological diseases; etiolgy, pathophysiology, types, diagnosis and treatment methods of “Gestational Trophoblastic Neoplasia”; A case report describing “Internal Jugular Vein Thrombosis in a 35-Year-Old Woman Developing Ovarian Hyperstimulation Syndrome During IVF Treatment” and robotic surgery used in the treatment of “Endometrial Cancer” are explained in detail.

We would like to express our endless gratitude to all those who contributed to the completion of our book titled “Gynecological Diseases and Treatment Methods”, the chapter authors, and the employees of “BİDGE” Publications. I hope our book will be beneficial to all readers.

01.07.2024

Assoc. Prof. Dr. Nursel ALP DAL

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CHAPTER I

Gestational Trophoblastic Neoplasia

İlhan DEMIR[1]

Introduction

Gestational Trophoblastic Neoplasia (GTN) is a disease that occurs in less than 1% of all tumors involving the female reproductive system in women of reproductive age. (Shahzadi et al., 2023). Gestational trophoblastic neoplasia (GTN) includes malignant entities of the gestational trophoblastic disease, including choriocarcinoma, invasive mole, epithelioid trophoblastic tumor (ETT), and placental site trophoblastic tumor (PSTT), all of which can metastasize and be fatal if not treated in time (Seckl et al., 2010).

Etiology

There are 3 types of trophoblastic cells, cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblasts. The abnormal

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proliferation of these cells causes gestational trophoblastic disease. Transformations of cytotrophoblasts and syncytiotrophoblasts produce hydatiform moles and choriocarcinoma. Intermediate trophoblasts are associated with PSTTs and ETTs(Ning et all., 2019).

Pathophysiology

Gestational trophoblastic neplasia results from aberrant fertilization. However, it is primarily the over-expression of paternal genes which results in the malignant potential of GTN(Davis et al., 1984). This was notified by John R Davis in 1984 when he found the Y chromosome in 9% of hydatidiform moles, 50% of invasive moles and 74% of choriocarcinoma patients(Davis et al., 1984). Apart from this, many genetic mutations have been identified as a potential for the development of GTN(Shih 2007). These include mutation in p53, p21, Rb, c-myc, c-erb-3, MDM-2, and EGFR over-expression(Tuncer et al., 2007). Because there are no activating mutations in the tyrosine kinase domain of epidermal growth factor receptors, conventional anti-epidermal growth factor receptor therapies have no role in the treatment of gestational trophoblastic neoplasia(Miyai et al., 2020).

Hydatidiform Mole

Hydatidiform moles, also called molar pregnancies, are benign trophoblastic tumors comprising approximately 80% of all gestational trophoblastic disease. Molar pregnancies are caused by abnormal gametogenesis and/or fertilization. These pregnancies are divided into two as complete and partial moles. Complete molar pregnancy occurs when an egg without a nucleus is fertilized by two sperm or a haploid sperm that

subsequently multiplies. Approximately 90% of complete moles have a 46XX karyotype, while 10% have a 46XY karyotype. The chromosomes of full moles are derived from the father; However, mitochondrial DNA comes from the mother(Ning et all., 2019).

Partial molar pregnancies are usually triploid (69XXX, 69XXY, or 69XYY) as a result of the fertilization of a haploid egg by two sperm or a haploid sperm duplicated during fertilization of a haploid egg. Diploid karyotypes resulting from the fertilization of an empty egg by two sperm may also be present. In the partial mole, both maternal and paternal DNA are usually expressed(Ning et all., 2019).

The frequency of molar pregnancy varies from less than 1 in 1000 pregnancies in developed countries to more than 1 in 400 in developing countries(Eiriksson et all., 2021)

Typical clinical signs of molar pregnancy include vaginal bleeding, hyperemesis gravidarum, early embryo loss, large uterus, early preeclampsia, symptoms of hyperthyroidism, and abdominal distension(Ngan et all., 2015). When a pregnant patient who is less than 20 weeks pregnant has signs and symptoms of preeclampsia, a full molar pregnancy should be suspected.

Nowadays, with increasingly sensitive home pregnancy tests and gynecology and obstetrics outpatient clinics equipped with transvaginal ultrasound, hyditadiform mole can be detected earlier, such as the first trimester, based on the patient's symptoms and ultrasound findings.

Molar pregnancies pose two serious threats to maternal morbidity and mortality: bleeding and neoplastic disease. Early

diagnosis and treatment before 12 weeks reduces the risk of bleeding(Eiriksson et all., 2021). Gestational trophoblastic neoplasia is diagnosed by serial hCG monitoring and imaging methods(Eiriksson et all., 2021). If there is elevation of serum hCG or evidence of metastases spreading to the pelvis, lung, or other organs outside the uterus, these patients are more likely to need treatment with chemotherapy(Ngan et all., 2018).

The most common form in patients with gestational trophoblastic disease is hydatidiform mole. The recommended first step in surgical treatment is uterine evacuation, but hysterectomy is also an acceptable alternative(Tidy et all., 2000). A meta-analysis found total hysterectomy after age 40 to have a significant advantage over uterine evacuation in preventing post-molar gestational trophoblastic neoplasia(Zhao et all., 2019) Uterine evacuation by drugs methods is not recommended(Tidy et all., 2000). The treatment approach should be shaped according to the patient's needs and wishes. Even if hysterectomy is chosen, patients should be aware that they will still need serial hCG monitoring because the development of gestational trophoblastic neoplasia requiring systemic therapy can also occur in those who have undergone hysterectomy(Zhao et all., 2019).

İnvasive Mole

Invasive mole is the invasion of molar tissue (partial or complete mole) into the myometrium or uterine vascular system (Tse et al., 2012). Enlarged villi and proliferative trophoblasts fill the myometrium, distinguishing it from choriocarcinoma(Tse et al., 2012). Pathologists mention the existence of villi in trophoblastic tissue(Wells et all., 2007). Generally, after removal of complete

moles and rarely after removal of partial moles, local invasive gestational trophoblastic neoplasia develops in 15% of patients and the metastatic form develops in 4% of patients(Seckl et al., 2000).

Human chorionic gonadotropin(HCG) level over 100,000 mIU/ml, theca lutein cyst over 6 cm, overgrowth of the uterus are considered as high risk for postmolar tumor formation and invasive disease development (Uberti et al., 2009). The most common symptom of invasive moles is persistent vaginal bleeding after molar pregnancy evacuation, but other symptoms are subinvolution of the uterus and persistent theca lutein cyst. Wells et. al., 2007). βHCG titresindeki artış, molar gebeliğin takibinde invaziv mol tanısı için bir laboratuvar testidir(Wells et al., 2007). Although the definitive diagnosis of invasive mole is made by pathology, invasive mole is also diagnosed with βHCG or radiological diagnosis(Green et al., 1996).

Choroiocarcinom

Choriocarcinoma develops from an abnormal trophoblastic population undergoing hyperplasia and anaplasia, most frequently following a molar pregnancy(Lurain et al., 2010). There are two types of choriocarcinoma: pregnancy-related and non-pregnancy-related. Pregnancy-related choriocarcinoma occurs after a previous miscarriage, after a hydatidiform mole, after normal pregnancy, or most commonly spontaneously, whereas non-pregnancy choriocarcinoma arises from pluripotent germ cells (Stockton et al., 2018).

Choriocarcinoma is a very rare neoplasm that occurs with variable frequency around the world(Lurain et al., 2010). The incidence of choriocarcinoma in Europe and North America is

estimated to be approximately 1 in 40,000 pregnancies and 1 in 40 patients with hydatidiform moles(Zhang et al., 2017). In Southeast Asia and Japan, the incidence of choriocarcinoma was found to be approximately 9.2 per 40,000 pregnancies and 3.3 per 40 patients with hydatidiform mole(Lurain et al., 2010). The development rate of choriocarcinoma in China was determined as 1 in 2882 pregnancies(Zhang et al., 2017). Asian, Native American, and African American women have a higher risk of developing choriocarcinoma than European and American women(Lurain et al., 2010). Risk factors other than race include older age, long-term oral contraceptive use, prior history of complete hydatidiform mole, and blood type A(Lurain et al., 2010).

The exact pathogenesis of choriocarcinoma is not fully understood, but studies have shown that cytotrophoblastic cells function as stem cells and undergo malignant transformation. Neoplastic cytotrophoblasts differentiate into intermediate trophoblasts and syncytiotrophoblasts (Mao et al., 2007). The mixture of cells mimics the normal development of the previllous blastocyst, a feature seen in other gestational trophoblastic neoplasms(Shih et al., 2007). Overexpression of p53 and MDM2 have been demonstrated in choriocarcinoma, with no evidence of somatic mutation. Other genes implicated with either overexpression or down-regulation via hyper-methylation include NECC1, epidermal growth factor receptor, DOC-2/hDab2, Ras GTPase-activating protein, E-cadherin, HIC-1, p16, and TIMP3. HLA-G is demonstrated at very high levels in choriocarcinoma and functions to change the tumor microenvironment through the inactivation of the local immune system(Shih et al., 2007).

Syncytiotrophoblasts, large eosinophilic smudgy multinucleated cells with known, large hyperchromatic nuclei, are intermixed with cytotrophoblasts, polygonal cells with distinct borders, and single irregular nuclei(Ali et al., 2009). Additionally, choriocarcinoma is an extremely vascular carcinoma characterized by necrosis and the absence of chorionic villi(Lurain et al., 2010)

Intraplacental choriocarcinoma shows trophoblast proliferation around the villi in the third trimester placenta and is usually normal in appearance (Heller et al., 2018).

Choriocarcinoma can be evaluated with many laboratory tests, including complete blood count (CBC), coagulation tests, body chemistries, kidney function panels, liver function panels, typing and screening, and quantitative hCG (Lurain et al., 2011).

The United Kingdom registers and follows all patients with hydatidiform molar pregnancies(Seckl et all., 2010). It uses the following criteria to start chemotherapy in gestational trophoblastic diseases: (Seckl et al., 2010):

- Plateaued or rising hCG following uterine evacuation
- Excessive vaginal bleeding
- Gastrointestinal or intraperitoneal bleeding
- Histologic evidence of choriocarcinoma
- Evidence of metastases in brain, liver, or gastrointestinal tract
- Lung opacities greater than 2 cm

- Serum hCG over 20,000 IU/L 4 weeks following evacuation
- High hCG after 6 months, even if it decreases after evacuation.

Following the diagnosis of choriocarcinoma, the healthcare professional should evaluate patients for metastasis; the lungs are the most common site for metastasis(Zhang et al., 2017). Chest, abdomen, and pelvic computed tomography are recommended in staging due to the highly metastatic nature of choriocarcinoma. Evaluate the brain via computer tomography or magnetic resonance imaging (MRI)(Lurain et al., 2011).

The World Health Organization has developed the following staging system for choriocarcinoma:(Seckl et al., 2010)

- Stage I: Disease confined to the uterus
- Stage II: Disease extending beyond the uterus, but confined to genital structures
- Stage III: Disease extending to the lungs
- Stage IV: Disease invading other metastatic sites

The International Federation of Gynecology and Obstetrics developed a scoring system by modifying the staging system of the World Health Organization**.**

Criteria

Furthermore, the patients are then stratified into low- and high-risk groups to determine treatment based on the following criteria:(Lurain et al., 2011)

Age

- 0: Younger than 39 years old
- 1: Greater than 39 years old

Antecedent Pregnancy

- 0: Mole
- 1: Abortion
- 2: Term

Pregnancy Event to Treatment Interval

- 0: Less than 4 months
- 1: 4 to 6 months
- 2: 7 to 12 months
- 4: Greater than 1 year

Pretreatment hCG (mIU/ml)

- 0: Less than 1000
- 1: 1000 to 10000
- 2: 10000 to 100000
- 4: Greater than 100000

Largest Tumor Mass

- 0: Less than 3 cm
- 1: 3 to 4 cm
- 2: Greater than 5 cm

Site of Metastases

- 0: None

- 1: Spleen, kidney
- 2: GI tract
- 4: Brain, liver

Number of Metastases

- 0: None
- 1: 1 to 4
- 2: 5 to 8
- 4: Greater than 8

Previous Failed Chemotherapy

- 0: None
- 2: Single-drug
- 4: Greater than 2 drugs

Cumulative Score

- Low-risk: Less than 7
- High-risk: Greater than 7

Low-risk gestational choriocarcinoma has almost 100% survival in women treated with chemotherapy, and high-risk gestational choriocarcinoma patients have 91% to 93% survival when utilizing multi-agent chemotherapy with or without radiation and surgery. Adverse risk factors making death more likely include stage IV disease or a cumulative score greater than 12 in women(Lurain et al. 2011).

Intra-placental choriocarcinoma with metastasis to the infant carries a very poor prognosis, with less than 20% survival(Lui et al. 2006).

Clinicians taking care of patients following molar pregnancy should remain aware and vigilant of the pitfall of heterophile (human anti-mouse) antibodies occurring in 3% to 4% of patients, resulting in falsely positive elevated hCG. The presence of heterophile antibodies can be teased out by serial dilution of serum, which will not show a parallel decrease with dilution or sending of serum and patient urine to a reference hCG laboratory.(Lurain et al., 2010).

High clinical suspicion should be maintained for choriocarcinoma in women with hemoptysis and molar pregnancy, current, or recent pregnancy, or irregular vaginal bleeding.(Zang et al., 2017)

PSTT

Gestational trophoblastic neoplasia (GTN) is a group of malignant neoplasms that arise from the placenta and mainly consisting of gestational choriocarcinoma (the most common), placental site trophoblastic tumor and epitelioid trophoblastic tumor (1-2% of all trophoblastic tumor). All these diseases mainly occur in the reproductive years, with a mean age of 30 years, except for a significant percentage of ETT observed in premenopausal and postmenopausal patients.(Hui et al., 2019)

Considering the past history of patients with PSST, approximately 50-67% occur after a normal pregnancy, 16-25% after a spontaneous miscarriage, and 16-50% after a hydatidiform mole, and the period between the previous pregnancy and clinical

symptoms can range from several months to 20 years. varies by(Hui et all., 2019). This makes differential diagnosis difficult. (Hui et al., 2019) (Hui et al., 2019)

Most common symptoms are vaginal bleeding and uterine enlargement, followed by amenorrhea and abdominal pain; both PSTT and ETT in 80% of the cases present mild to moderate elevation of serum human chorionic gonadotropin (hCG) (values ranging from 5 to 26000 mIU/mL), while GC has typical high levels of this hormone in all patients. Another difference between GC and the others concerns rates of recurrence and metastasis: while only 25-30% of the patients with PSTT or ETT show recurrence or metastasis, GC can present early metastases that can involve lung, liver, spleen, kidney, bowel, and brain.(Zampacorta et al., 2023)

Clinical suspicion may arise from symptoms, serology, pelvic ultrasound examination and/or other radiological examinations; hysterocolposcopy and biopsy are required for the diagnosis of certainty.(Lukinovic et al., 2022)

Grossly, PSTT is a well circumscribed, nodular, round, solid mass of 1 to 10 cm in size with cut surface usually solid and fleshy and a white-tan to light yellow color. Generally, involves the endomyometrium but deep myometrial invasion is seen in 50% of cases, transmural myometrial invasion and involvement of sierosa is seen in 10% of the cases, rarely with extension into the broad ligament and adnexa. Focal hemorrhage and necrosis are seen in nearly 50% of cases. On the other hand, GC and ETT present a deep invasion of surrounding structures, especially GC that is a bulky, dark red, solid, friable, destructive uterine mass with hemorrhage,

necrosis, and deep myometrial invasion up to uterine perforation.(Zampacorta et al., 2023)

Microscopic analysis in PSTT reveals implantation site neoplastic intermediate trophoblasts, i.e., large, polyhedral to round, often mononucleated cells predominately aggregated into cords, nests and sheets with infiltrative growth pattern: characteristically these cells infiltrate the myometrium by separating individual muscle fibers and their vascular invasion pattern recapitulates that of normal implantation trophoblast. In fact, in more than two-thirds of cases tumor cells replace the wall of myometrial vessels and these transformed blood vessels are unique among all human solid tumors and allow PSTT diagnosis. Therefore, PSTT has a characteristic monophasic cell population consisting of neoplastic intermediate trophoblasts unlike triphasic GC that presents syncytiotrophoblast, cytotrophoblast, and intermediate trophoblast components. Furthermore, GC shows greater cytologic pleomorphism, higher mitotic index and more extensive hemorrage and necrosis than PSTT with infiltrative or solid destructive growth and common lymphovascular tumor thrombi.(Zampacorta et al., 2023)

ETT can be distinguished from PSTT by some unique pathological features, such as the presence of eosinophilic hyaline-like material in the center of some tumor nests (simulating keratin formation), diffuse or “geographic” necrosis, scattered decidualized benign stromal cells around the tumor(Zampacorta et al., 2023).

In PSTT, immunohistochemical stainings for epithelial markers (CKAE1/AE3 and CK18), hPL, MUC4, HSD3B1, HLA-G, MEL-CAM (CD146), CD10, GATA3 and PDL1 are positive. Inhibin and hCG are positive only in scattered multinucleated tumor

cells and the proliferative index evaluated with Ki-67 is equal to 10-30% of the neoplastic cells. On the other hand, in ETT, MEL-CAM and hPL are expressed only in individual cells while inhibin is diffusely positive in tumor cells; lastly, GC presents several staining patterns based on different types of neoplastic cells (syncytiotrophoblasts, cytotrophoblasts and intermediate trophoblasts), but the diagnostic key is the high mitotic index (Ki-67 > 90%) with a diffuse positivity for hCG.(Feng et al., 2019)

ETT

Epithelioid trophoblastic tumor (ETT) is the rarest subtype of gestational trophoblastic neoplasia (GTN) accounting 1.0%–2.0% of all GTN cases.(Li et al., 2011) Shih and Kurtmann first reported on the clinical and pathological features of ETT in 1998, and since 2003 the World Health Organization has accepted the classification of the tumor as a form of GTN.(Lybol et al., 2011) ETT can arise from all types of pregnancy, including full-term delivery, miscarriage, ectopic pregnancy, or following a hydatidiform mole. The clinical presentations include mostly, vaginal bleeding and slightly elevated ß-serum chorionic gonadotropin (ß-hCG) levels.(Shih et al., 2007)

Almost half of the cases occur in the cervix or the lower uterine segment forming a well-defined, expandable mass. The tumor appears as a discrete, nodular, expansile lesion with solid, cystic, and hemorrhagic components. The gross size varies from 0.5 to 5 cm(Allison et al., 2006). Microscopically the growth pattern of ETT is nodular and well-circumscribed with focally infiltrative at the periphery.(Lanjevar et al., 2022). The cells are relatively uniform, mononucleate arranged in nests and cords, the predominant cell type

being chorionic-type intermediate trophoblast. Also, compared to placental trophoblastic tumors and choriocarcinoma, calcification is common in epithelioid trophoblastic tumors.(Lanjevar et al., 2022). Mitoses are reported to range from 0-9/10 high-power fields with a mean of 2/10 and the Ki-67/MIB1 proliferative index ranges from 10%–25%(Allison et al., 2006). Immunohistochemically, ETT has diffuse expression of HLA-G, p63, inhibin, cyclin E, HSD3B1, GATA3(Lanjevar et al., 2022). Other trophoblastic markers including Mel-CAM and hPL are focally positive.(Lanjevar et al., 2022).

ETT has a high resistance to single-agent chemotherapy and a mortality rate of 10% to 24% for poor prognosis, requiring multiagent therapy(Lybol et al., 2011). The current standard of care focuses on total abdominal hysterectomy bilateral salpingo-oophorectomy, lymphadenectomy, and resection of areas of residual disease following multiagent chemotherapy in early-stage disease(Shih et al., 2011).

Surgery combined with chemotherapy is recommended for patients with metastatic disease. Despite the rarity of ETT with a small number of cases in analyses, it is difficult to establish a management strategy for patients with this disease. In our opinion, the future treatment of ETT could be by immunotherapy, investigational studies on biological agents targeting molecules like EGFR, VEGF, PD-1, PD-L2, CD-105, and LPCAT1 are required, especially in resistant chemotherapy disease.(Gorun et al., 2022)

Treatment of Low Risk Gestational Trophpblastic Neoplasia

The main chemotherapeutics used in single-agent treatment of low-risk GTN are methotrexate and dactinomycin. Debate

continues regarding the most effective treatment regimen, including primary cure rates, patient recovery and quality of life, side effect profiles, and cost.

The Gynecologic Oncology Group conducted a randomized controlled trial of dactinomycin administered every 2 weeks (1.25 mg/m^2 maximum dose 2 mg) versus weekly methotrexate (30 mg/m^2) and found that dactinomycin administered every 2 weeks compared with methotrexate by 70%. It concluded that it showed superiority with a complete response rate of 53%(Osborne et all., 2011). Overall, there are no major differences in the toxicity and side effect profiles of methotrexate and dactinomycin. The most common side effects are nausea, fatigue and anemia. However, while alopecia is more common with dactinomycin, stomatitis is more common with methotrexate(Lawrie et all., 2016).

Hysterectomy may be recommended for patients with stage I disease and no desire for children, but permanent disease may occur after surgery and systemic treatment may be necessary(Bolze et all., 2018). A retrospective study showed that 82% of women with non-metastatic, low-risk gestational trophoblastic disease who underwent hysterectomy did not need chemotherapy(Bolze et all., 2018). Curettage may be recommended for patients under 35 years of age with a WHO prognostic score below 5. This approach can save more than 40% of patients without the need for chemotherapy and has a low incidence of complications such as uterine perforation or acute bleeding(Osborne et all., 2016). Drug therapy is continued until serum hCG levels return to normal, followed by consolidation therapy for 4 to 6 weeks(McGrath et all., 2010). Cure rates approach 100% in patients with low-risk disease.

Treatment of High Risk Gestational Trophoblastic Neoplasia

High-risk gestational trophoblastic neoplasia is treated with combination chemotherapy. Two commonly used regimens with high cure rates and acceptable toxicity profiles are etoposide, methotrexate, dactinomycin, cyclophosphamide, vincristine (EMA-CO) and etoposide, methotrexate, dactinomycin, etoposide, cisplatin (EMA-EP). Patients with liver and brain metastases and a WHO score above 12 are considered ultra-high risk. These patients may die during treatment due to acute bleeding or complications of disseminated disease. After normalization of serum hCG, consolidation therapy continues for 8 weeks(Cyriac et all., 2011).

Reccurrent Gestational Trophoblastic Neoplasia

Recurrence of gestational trophoblastic neoplasia requires restaging with computed tomography scan of the head, chest, abdomen, and pelvis(Mapelli et all., 2013). Fluorodeoxyglucose positron emission tomography may be useful in localizing refractory or recurrent disease foci and planning treatment(Mapelli et all., 2013).

The disease must be re-scored using the WHO staging system, and treatment options for those at high risk include EMA-EP, EMA-CO, ICE(ifosfamide, carboplatin, etoposide) protocols(FIGO 2009).

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CHAPTER II

Case Report: Internal Jugular Vein Thrombosis in a 35-Year-Old Woman Developing Ovarian Hyperstimulation Syndrome During IVF Treatment

Mesut ALÇI[1]

Introduction:

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication that can occur in women undergoing controlled ovarian stimulation for IVF. OHSS is characterized by ovarian enlargement and fluid shift from the intravascular space to the third space, leading to ascites, pleural effusion, and thromboembolic events. Thrombosis, although rare, is a significant complication associated with OHSS due to increased blood viscosity and a hypercoagulable state.

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Case Presentation:

A 35-year-old woman with an eight-year history of infertility received IVF treatment at an external center. Eight days after the transfer, she presented to our Emergency Department with complaints of abdominal pain and distension. Physical examination revealed significant abdominal distension, and the patient developed moderate OHSS symptoms such as nausea, vomiting, and shortness of breath. Transabdominal ultrasound showed bilateral hyperstimulated ovaries extending above the umbilical level, with each ovary approximately 30 cm in diameter. There was widespread ascites with about 5 cm of free fluid, and echogenic fluid was observed in the splenic and hepatic regions. The patient also had pleural effusion, and her oxygen saturation was around 88%. She was admitted to the Intensive Care Unit (ICU) for monitoring and was started on high-flow nasal oxygen.

Intravenous hydration, electrolyte management, and therapeutic anticoagulation with enoxaparin (80 mg daily) were administered. Due to her respiratory symptoms, she remained in the ICU for four days. After hydration, anticoagulation, and antibiotic therapy, the patient was transferred to the ward for further monitoring. Over the next 10 days, patients symptoms improved, and a follow-up thoracic ultrasound showed no effusion, though the hyperstimulated appearance of the ovaries persisted. An intrauterine gestational sac was observed, and the patient was discharged with prophylactic anticoagulation after a total of 14 days, including four days in the ICU.

One week after discharge, the patient had no additional complaints. However, three weeks later, she presented to our clinic

with sudden neck swelling and pain on the right side, accompanied by low-grade fever. Physical examination revealed neck swelling with mild warmth. Neck ultrasound and Doppler ultrasound were performed, revealing a thrombus in the right internal jugular vein. Based on this finding, the patient was readmitted, and the enoxaparin dose was increased to therapeutic levels (1 mg/kg twice daily). She was closely monitored for pulmonary embolism and other thromboembolic complications. After 10 days of therapeutic enoxaparin, the thrombus in the IJV recanalized. The patient continued therapeutic enoxaparin for two more weeks before transitioning to a prophylactic dose.

Laboratory tests for lupus anticoagulant, anticardiolipin antibody, antinuclear antibody, anti-DsDNA, thrombophilia gene panel (MTHFR heterozygous), BCL-ABL, activated protein C and S, JAK-2 gene, and homocysteine levels were ordered, revealing only MTHFR heterozygosity. An anatomical scan detected a single umbilical artery anomaly. At 31 weeks, fetal growth restriction was noted, and the patient was admitted to our clinic. Betamethasone was administered, and hydration was provided. The patient was monitored twice weekly with Doppler studies and underwent an emergency cesarean section at 35 weeks due to oligohydramnios, delivering a girl weighing 1940 grams with an APGAR score of 8/8.

Discussion:

The development of IJV thrombosis in the context of OHSS is a rare but serious complication. Its pathophysiology involves multiple factors, including hemoconcentration, elevated circulating estrogen levels, and increased vascular permeability, all contributing to a procoagulant state. OHSS can be classified as mild, moderate,

severe, or critical based on clinical symptoms and laboratory findings. In this case, the patient had moderate to severe OHSS, putting her at higher risk for thromboembolic events. Despite prophylactic anticoagulation, the development of IJV thrombosis indicates that standard prophylactic measures may be inadequate in some high-risk cases, emphasizing the importance of individualized anticoagulation strategies for patients with severe OHSS.

The treatment of IJV thrombosis involves therapeutic anticoagulation and supportive care. In this case, the patient responded well to increased enoxaparin doses, showing gradual improvement in symptoms and resolution of the thrombus as confirmed by follow-up Doppler ultrasound.

Conclusion:

This case highlights the importance of recognizing the risk of thromboembolic events in patients undergoing IVF treatment, particularly those with OHSS. Careful monitoring and potentially more aggressive anticoagulation strategies may be necessary for high-risk patients. Further research is needed to establish optimal protocols for preventing and managing thromboembolic complications associated with OHSS.

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CHAPTER III

Robotic Surgery in Endometrial Cancer

Varol GÜLSEREN

1. Introduction

Endometrial carcinoma (EC) is the fourth most common cancer in women worldwide, and the most common gynecological malignancy in the developed countries (Padmanabhan & al., 2019). The majority of cases have endometrioid histology corresponding to estrogen-dependent. Fortunately, most new diagnoses of EC are early-stage, low-grade disease, with have excellent survival. The first step and cornerstone in the management of endometrial cancers is surgical staging according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 (Creasman, 2009). Traditionally, laparotomy have been the procedure of choice. However increasingly minimally invasive surgical methods have been used in the last two decads. In addition to, many surgeons find it difficult to master the laparoscopic approach due to its responsive movements and abutment effects and do not offer it to most of their patients. This computer-assisted minimally invasive surgery has

been called “robotic surgery” and with this method, the above mentioned difficulties can be overcome in laparoscopy.

Obesity is a well-known risk factor for developing EC. Mortality for survivors is significantly more likely to be related to obesity-related comorbidities. Obesity and EC, likely interacting with each other, are augmenting in the Western world (Flegal & al., 2016). Therefore this subgroup will proceed to be a defiance for gynecologic oncology surgeons. Nevertheless, robotic surgery increasingly the method of choice in the obese population (Lindfors & al., 2020). Minimal invasive surgery appears to provide equivalent outcomes in terms of survival compared with laparotomy, with further advantages: shorter length of stay, less use of pain killers, lower rate of complications, and improved quality of life.

The standard surgical approach for FIGO stage I EC withstand of total hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy (Bartosch & al., 2017). In general, literature datas recommend a complete surgical staging for intermediate high-risk endometrioid cancer (FIGO stage IA G3 and IB) (Bartosch & al., 2017). Lymphadenectomy could be important in assigning a case’s prognosis and in tailoring adjuvant treatments. In the studies, it is found that have failed to show a overall survival (OS) or disease-free survival (DFS) benefit in stage I endometrial cancer (Benedetti & al., 2008; Kitchener & al., 2009). The role of systematic lymphadenectomy is an issue of current controversy. Conventionally, the surgical approach for stage II EC consists of total hysterectomy with salpingo-oophorectomy and systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy (Bartosch & al., 2017).

2. The Application of Robotic Surgery in Endometrial Cancer

A surgical robot is a computer-controlled system that can be programmed to assist the surgeon in the application and manipulation of surgical instruments. This system permits the surgeon to operate from a console that is remote from the operative table. This system was initially planned for implementation by the military to provide immediate surgical capability on the battlefield for a surgeon located at a site remote from the injured service member (telesurgery) (Satava, 2003). The first robotic-assisted gynecologic surgery was performed in 1998 (Falcone, 1999). The benefits of robotic surgery are similar those of conventional laparoscopy. In addition to, robotic surgery have advantages of overcoming several barriers to the use of laparoscopy. Robotic machine has three parts: 1- surgeon's console, 2- patient cart, 3- optical cart. Surgeon's console contains 3-dimensional monitor and joysticks which control the instruments. A three-dimensional view of the operative field is provided with the stereoscopic, binocular viewer. Patient cart has four arms for the instrument and camera. The robot allows for 7° of motion vs. the limited 4° of motion in laparoscopy. The robotic arms imitate the movements of the surgeon's hand. The surgeon is able to perform traditional laparoscopic procedures to include: grasping, cutting, manipulating tissues, dissecting, cutting, suturing, and coagulating.

After placing the patient in the lithotomy position, the uterine manipulator is fixed inside the cervical and uterine cavity. Helps manipulate the uterus intraoperatively. With the optical trocar, a 12 mm camera port is placed 3 cm above the belly button in the midline. The rest of the ports are placed after the abdomen is inflated with

gas. A 0^0 degree camera is usually used except for the paraaortic lymphadenectomy (used 30^0 degree camera) step of the operation.

Robotic surgery compared to conventional laparoscopy (table 1):

Advantages: Binocular three-dimensional high-definition immersion view, seven degrees of freedom permitted with the wristed instruments (Improved dexterity, provides a better precision of movement without tremor, intuitive instrument movement), easier to complete radical and morbid surgeries, improved ergonomics for the surgeon, easier suturing, a shorter learning process.

Disadvantage: Lack of tactile perception, increased cost, risk of intraoperative mechanical failure, need for additional trained staff.

In the literature, it is shown that the operation time in patients with EC was significantly longer in the robotic surgery group than in both of the laparoscopic and laparotomy group (Aiko & al., 2020; Wang & al., 2020; Ind & al., 2017). Estimated blood loss is found the similar between robotic surgery group and laparoscopic surgery group but was significantly less in the robotic surgery group than in the laparotomy group (Wang & al., 2020; Park & al., 2016). In consistent with these results, there are studies showing that the estimated blood loss in robotic surgery is higher than laparoscopic surgery (Aiko & al., 2020). Length of stay was found shorter in robotic surgery than laparoscopic surgery and laparotomy (Aiko & al., 2020; Wang & al., 2020; Park & al., 2016).

Table 1. *Comparison of robotic surgery with laparoscopy*

Advantages	**Dis-advantages**
- Binocular three-dimensional high-definition immersion view, - Seven degrees of freedom permitted with the wristed instruments (Improved dexterity, provides a better precision of movement without tremor, intuitive instrument movement), - Easier to complete radical and morbid surgeries, - Improved ergonomics for the surgeon, - Easier suturing, - Shorter learning proces	- Lack of tactile perception, - Increased cost, - Risk of intraoperative mechanical failure, - Need for additional trained staff.

3. Obesity

There are several reasons to operate with robotic surgery in EC patients. One of the most important reasons is that most EC patients are obese. About 65% of patients is obese (Lindfors & al., 2020). Wound infection and difficult management of laparoscopy or laparotomy in patients with obese are major factors in robotic surgery selection.

Obese cases may not be submitted standard surgical procedure to the same extent as the general population, partly due to surgeons' bias (Lindfors & al., 2020). Studies have shown that obesity increases the risk of surgical morbidity regardless of the surgical method, but minimally invasive surgerys significantly reduce the risk compared to open surgery (Gunderson & al., 2014; Bouwman & al., 2015). Nevertheless, obese cases are known to be a technical challenge due to compromised surgical access. Against this, in the some study, there were found that it is no significant

difference in term of the number of pelvic nodes, operation time, estimated blood loss or length of hospital stay between the patients with obese and non-obese (Zhao & al., 2020). In a study of patients with endometrial cancer with morbidly obese (body mass index> 40), there were found that there was no difference in laparotomy and robotic surgery groups in terms of intraoperative, postoperative complication and wound infection (Fornalik & al., 2018). Pelvic and paraaortic lymph node dissection numbers were similar between the groups (Fornalik & al., 2018). It was found that the estimated blood loss was less in the robotic surgery group and the total operation time was less in the laparotomy group (Fornalik & al., 2018). In the study by Lindfors et al., there was a significantly lower blood loss, lower need for transfusions, shorter operating time, and shorter postoperative stay in hospital in the robotic group than open surgical group at obese cases (Lindfors & al., 2020). In addition to, it find that there was a significant difference in OS, in favor of robotic compared to open surgery (Lindfors & al., 2020).

4. Oncologic outcomes and effectiveness on survival

The adequacy of lymphadenectomy is very important for surgical staging in endometrial cancer. In the previous studies, they are shown that the number of pelvic and paraaortic lymph nodes taken was similar in patients who underwent between robotic surgery and laparoscopic surgery or laparotomy (Aiko & al., 2020; Wang & al., 2020; Ind & al., 2017; Gracia & al., 2020). When the elderly (>70 years) and younger patients were compared, no difference was found between the number of pelvic and para-aortic lymph nodes received (Hotton & al., 2020).

Although the adequacy of lymphadenectomy is very important, it does not fully reflect the survival. In the previous studies, it is found that no difference in five year OS was found between the open surgery and robotic surgery groups (Park & al., 2016; Song & al., 2020; Lindfors & al., 2018). However, five year DFS was significantly higher in the laparotomy group than in the robotic group (Park & al., 2016; Song & al., 2020). Comparing laparoscopy and robotic surgery, in the previous study, it is shown that both DFS and OS do not vary with the surgical approach (laparoscopycal and robotic) (Park & al., 2016; Corrado & al., 2018). In the study comparing patients undergoing single port laparoscopy, multiport laparoscopy and robotic surgery, it was shown that there was no difference between the groups between disease-free and OS (Chambers & al., 2019). In the meta-analysis, it evaluated mortality rates of patients with underwent hysterectomy for any type of gynecological malignancy: mortality rate for laparoscopy is 1/281 (1/169−1/469) and mortality rate for robotics is 1/476 (1/365−1/620) (Behbehani & al., 2019). The effect of robotic surgery and other interventional methods on the efficiency of the surgery was given in table 2.

Table 2. *The effect of robotic surgery and other interventional methods on the efficiency of the surgery*

	No. of patients	Recurrence	OS (5 years)	Intraoperative complication
Lindfors A. Et al (5) 2020	LT: 86 R: 131	LT: 17.4% R: 9.9%	LT: 75.6% R: 87.0% P: 0.02	LT: 0 (0%) R: 5 (3.8%) P: 0.55
Chambers L. et al. (24) 2019	LS: 496 R: 645		LS: 91.8% R: 90.7% P: 0.99	
Song J. Et al (21) 2020	LT: 58 R: 77	LT: 0% R: 10.4%	LT: 94.2% R: 95.5% P: 0.51	
Aiko K. Et al (11) 2020	LS: 102 R: 121			LS: 2 (2%) R: 1 (0.8%) P: 0.19
Lindfors A. Et al (22) 2018	LT: 137 R: 141		LT: 69% R: 77% P: 0.29	LT: 1 (1%) R: 6 (4%) P: 0.13
Corrado G. Et al (23) 2018	LS: 406 R: 249	LS: 8.2% R: 6.8% P:	LS unspecified R unspecified P: 0.79	LS: 9 (2.2%) R: 8 (3.2%) P: 0.43
Fornalik H. et al (18) 2018	LT: 35 R: 76			LT: 0% R: 7% P: 0.18
Lee HJ. et al (35) 2018	LS: 16 R: 26			LS: 12.5% R: 11.5% P: 1.0
Chan JK. et al. (36) 2015	LT: 567 LS: 98 R: 422			LT: 22.6% LS: 13.3% R: 8.3% P< 0.01

LN: Lymph node DFS: Disease Free-Survival OS: Overall Survival

R: Robotic surgery LS: Laparoscopic surgery LT: Laparotomy

5. Sentinel node mapping

Patients with metastatic EC have a much poor prognosis. Most common metastatic locations include intra-abdominal organs and lymph nodes. There is important accurately assign FIGO surgical stage to choosing to appropriate adjuvant therapy. Therefore, pelvic and paraaortic lymphadenectomy is often recommended to allow for complete pathologic nodal assessment. Nevertheless, in a largely low-risk endometrial cancer population,

trials had not found any survival benefits for surgical nodal evaluation as well as can resulted acut and chronic complication. Workings has been made to limit the extent of lymphadenectomy to minimize chronic long-term leg edema impairing patients' quality of life side effects by the application of sentinel lymph node (SLN) mapping algorithm with success. In a study of patients undergoing SLN mapping with robotic surgery, applying the SLN algorithm, positive nodes were detected in 91.3% (sensitivity) and the negative predictive value was 98.8% (Backes & al., 2019). Robotic approach as minimally invasive surgery may be preferred in sentinel lymph node sampling, to reduce bleeding and lymphatic disruptions and interventional processing.

6. Complications and long-term effects

Acute - chronic complications and their effects on long-term general health in the evaluation of robotic surgery performed in EC patients suggest that the selection of this method should increase over time. When evaluated in terms of intraoperative complications (intestinal injury, bladder injury, vaginal laceration, intraoperative bleeding> 500 ml, and inferior vena cava injury), there were significantly fewer intraoperative complications in the robotic surgery group than in both of the laparoscopic surgery and laparotomy group (Wang & al., 2020; Park & al., 2016). Some studies shown that there was significantly less blood transfusion in the robotic surgery group than laparoscopic surgery and laparotomy (Wang & al., 2020, Ind & al., 2017; Matern, Kang & Lim, 2020). However, despite this difference, there was no significant difference in blood transfusion use and postoperative hemoglobin concentration awareness (Ind & al., 2017). Nevertheless, in robotic surgery, the time of surgery was found to be higher than laparoscopic

surgery (Aiko & al., 2020). However, at the end of the learning curve, this difference may be reduced and perhaps closed.

When evaluated in terms of postoperative complications (deep vein thrombosis, pulmonary embolism, intestinal obstruction, fever, vaginal cuff infection, pelvic abscess, wound infection, hernia, vaginal cuff dehiscence, and lymphedema), there was no found difference between robotic surgery and laparoscopic surgery (Aiko & al., 2020; Wang & al., 2020; Park & al., 2016). Postoperative complication was less in robotic surgery than laparotomy (Wang & al., 2020; Park & al., 2016). However, when postoperative complications were evaluated in some studies, there was no difference between laparotomy and robotic surgery (Padmanabhan & al., 2019; Ind & al., 2017; Lindfors & al., 2018). Also, there was no difference between the laparotomy and robotic surgery groups in terms of pain scores or use of post-operative analgesia (Ind & al., 2017). On the basis of the available literature, datas suggested a low incidence of postoperative symptomatic venous thromboembolism after robotic-assisted hysterectomy in obese patients with endometrial cancer and it is found that there seems to be no clear clinical or economic justification for the universal use of thromboprophylaxis (Carbajal-Mamani & al., 2020; Laskov & al., 2018). We agree the decision of thromboprophylaxis should be made on a case-by-case basis. In previous studies, neither intraoperative nor postoperative complications differed between normal weight and obese, elderly and younger patients (Aiko & al., 2020; Gracia & al., 2020; Hotton & al., 2020).

Long-term results of robotic surgery have serious impressions on quality of life and social life. General health and

social functioning, postoperative robotic surgery group was found to be significantly better than open surgery (Lundin & al., 2019). No significant difference was found in physical functioning, bodily pain, vitality, role emotional and mental health (Lundin & al., 2019). In the study where sexual health measures were evaluated in patients operated for endometrial cancer; it is shown that there were no significant differences in the quality of life and sexual health measures between the laparoscopic and robotic groups at baseline or specific time point post-surgery (Ferguson & al., 2018). Furthermore, there was no increase in the possibility of developing urinary incontinence in patients undergoing robotic surgery (Lipetskaia & al., 2019). Intraoperative and postoperative complications and long term results of robotic surgery are given in table 3.

7. Learning Curve

Robotic-assisted surgery is also associated with a shorter learning curve which enables more surgeons to do minimally invasive surgery for endometrial cancer (Padmanabhan & al., 2019). Investigation of operative time for robotic-assisted hysterectomy with lymphadenectomy with respect to chronologic order of each group of 20 cases demonstrated a decrease in operative time (Wang & al., 2020). However, For the groups with laparoscopic and laparotomy, there was no difference in operative time with respect to chronologic group order of cases (Wang & al., 2020). It was concluded that the learning curve for robotic-assisted surgery seems to be easier compared with that for laparoscopic surgery for surgical management of endometrial cancer.

Table 3. *Complications of robotic surgery*

	Compared to LS	Compared to LT
Intraoperative complications		
Intestinal injury	+[12,14]	+[12,14]
Bladder injury	+[12,14]	+[12,14]
Vaginal laceration	+[12,14]	+[12,14]
Intraoperative bleeding (> 500 ml)	+[12,14]	+[12,14]
Inferior vena cava injury	+[12,14]	+[12,14]
Blood transfusion	+[12,13,27]	+[12,13,27]
Postoperative complications		
Thrombosis, pulmonary embolism	N/A[11,12,,14,19,23]	+[12,14] , N/A[1,13,22]
Intestinal obstruction	N/A[11,12,,14,19,23]	+[12,14] , N/A[1,13,22]
Fever	N/A[11,12,,14,19,23]	+[12,14] , N/A[1,13,22]
Infection, Abscess	N/A[11,12,,14,19,23]	+[12,14] , N/A[1,13,22]
Hernia	N/A[11,12,,14,19,23]	+[12,14] , N/A[1,13,22]
Lymphedema	N/A[11,12,,14,19,23]	+[12,14] , N/A[1,13,22]
Long-term results		
General health and social functioning		+[30]
Physical functioning, bodily pain		N/A[30]
Role emotional and mental health		N/A[30]
Quality of life	N/A[31]	N/A[31]
Sexual health measures	N/A[31]	N/A[31]
Urinary incontinence	N/A[32]	N/A[32]

LS : Laparoscopy , LT: Laparotomy,

"+" : Less complications in robotic surgery, "-" : More complications in robotic surgery, "N/A" : No significant difference

8. Disadvantage-Cost

An important concern raised about robotic surgery relates to the high costs associated with the operation linked mainly to maintenance costs and operating room time; however, research has shown that the latter of these two factors becomes insignificantwith improved surgeon experience (Matern, Kang & Lim, 2020). The total costs one-year post-surgery from hospitalization, primary sector visits, outpatient visits and prescription drugs were higher per patient in the robotic surgery group (Korsholm & al., 2019). According to the metaanalysis results obtained with the data of many studies, robotic surgery was found to be more costly (Ind & al.,

2017). However, in EC staging with underwent robotic surgery, was associated with significantly lower medicine and material costs attributed to intravenous fluids, analgesia, antiemetics and length of stay than open surgery (Agarwal, Rajanbabu & Unnikrishnan, 2018). In the other study, it is found that costs for surgery and direct postoperative care did not differ significantly between the laparotomy and robotic surgery groups (Lindfors & al., 2018).

9. Conclusion

The effectiveness and oncological results of surgery in robotic surgery in endometrial cancer appear to be similar to other surgical methods. It has been stated that it has generally better results than other methods for intraoperative complications. The learning curve has been reported to be shorter than laparoscopic surgery. When all features are evaluated, robotic surgery may be the first method of choice especially for early stage endometrial cancer and obese patients.

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CHAPTER IV

Yardımcı Üreme Teknolojisinde Kullanılan Overyan Stimulasyon Stratejilerinin Yeniden Değerlendirilmesi

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Giriş

Yardımcı üreme teknolojisi (YÜT), 1978 yılında ilk in vitro fertilizasyon (IVF) bebeğinin doğumundan bu yana hızla ilerlemiştir ve ilk IVF tedavisi uyarılmamış bir siklus ile gerçekleştirilmiştir. Bir IVF tedavi döngüsünün amacı, hasta güvenliği, tedavi yan etkileri ve maliyet gibi faktörleri dikkate alarak, tek bir oosit toplama prosedüründen hem canlı doğum olasılığını hem de kümülatif canlı doğum oranını en üst düzeye çıkarmaktır.

Overyan stimülasyon, IVF tedavi sürecinde kritik bir adımdır çünkü oosit toplama sırasında toplanan oosit sayısı, canlı doğum

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şansının daha yüksek olmasıyla ilişkilendirilir. IVF tedavisi gören hastalarda, oosit verimini en üst düzeye çıkarmak için çeşitli overyan stimülasyon protokolleri geliştirilmiş ve tasarlanmıştır. Bununla birlikte, YÜT için overyan stimülasyonunun en ciddi ve yaşamı tehdit eden komplikasyonlarından biri olan overyan hiperstimülasyon sendromu (OHSS) riskinde artış görülmektedir. Son on yılda, hafif (mild) stimülasyon protokolleri daha yüksek bir güvenlik profiline sahip oldukları ve mukayese edilebilir reprodüktif sonuçlarla (Nargund vd., 2017) ilişkili oldukları için popülerlik kazanmıştır.

Overyan stimülasyonu için ön tedavi

Ön tedavi, planlanan over stimulasyonu siklusundan hemen önceki siklusta hormon tedavisinin kullanılmasını ifade eder. Hem östrojen hem de progestojen içeren kombine oral kontraseptif haplar (KOK), sadece östrojen veya sadece progestojen preparatları dahil olmak üzere farklı oral ön tedavi hormon türleri vardır. Ön tedavi aşağıdaki durumlarda kullanılmaktadır.

1.Overyan yanıtı iyileştirmek

Ön tedavi, spontan luteinizan hormon (LH) pikinin oluşmasını önleyerek, antral folikül sayısını artırarak, foliküllerin gelişimini senkronize ederek ve oositlerin kalitesini artırarak düşük overyen yanıtı (DOR) olan hastalarda gonadotropinlere olan yanıtı iyileştirebilir (Orvieto, 2022)

Sadece östrojen ön tedavisi, KOK haplara kıyasla folikül uyarıcı hormonun (FSH) daha hafif bir şekilde baskılanması ile antral folikül çapında daha az bir azalmaya neden olduğu için popülerlik kazanmaktadır (Fanchin, 2003; S. Zhang vd., 2022)

2.Senkronizasyon

Ön tedavi, luteal-foliküler geçiş sırasında FSH seviyelerinin aşırı yükselmesini önleyerek foliküler gelişimin senkronize edilmesine yardımcı olabilir. Bu durum erken antral foliküllerin katılımını ve siklusun erken dönemlerinde bir veya daha fazla dominant folikülün erken gelişimini önleyerek stimülasyon sırasında asenkronize folikül gelişimini engeller. (Gonen vd., 1990) .Bu durum, bazal FSH seviyeleri yüksek olan kadınlarda ve gonadotropin salgılatıcı hormon (GnRH) antagonisti protokolü kullanılan kadınlarda daha yaygın görülür, çünkü bu protokolde siklusun erken dönemlerinde, gonadotropin stimülasyonundan birkaç gün sonra GnRH antagonisti eklenene kadar, yeterli hipofiz down regülasyonu sağlanamamaktadır. Yapılan çalışmalar östradiol ile ön tedavinin GnRH antagonist protokolünde folikül senkronizasyonunda etkili olduğunu göstermiştir (Saple vd., 2016; Zhu vd., 2022). Daha önceki sikluslarda asenkronize folikül gelişimi nedeniyle suboptimal sonuç alan kadınlarda ön tedavi düşünülebilir.

3.Planlama

Hormon tedavisinin süresini ayarlamak tedavi döngüsünün başlama zamanlamasında esnekliğe olanak verdiğinden siklusun başlangıcını kontrol etmeye yardımcı olur.(Barmat vd., 2005; Gonen vd., 1990; J. A. Huirne vd., 2006).Polikistik over sendromu (PKOS) olan hastalarda genellikle oligomenore veya amenore görüldüğünden, ön tedavi genellikle bu hastalarda siklusun başlangıcını planlamak (menstrüasyonu başlatmak) için kullanılır. KOK haplar veya progesteron, bu amaçla PKOS olan hastalarda yaygın olarak kullanılmaktadır ayrıca yüksek endojen LH seviyelerini baskılamaya da yardımcı olurlar. (Wei vd., 2017) .

4.Over kisti oluşumunu azaltma

Ön tedavi, özellikle GnRH agonist protokolünde alevlenme etkisi nedeniyle, siklusun başında over kisti oluşumunu azaltmaya yardımcı olabilir. KOK haplar ile ön tedavinin, GnRH agonist tedavisinin süresini kısalttığı ve ihtiyaç duyulan gonadotropin miktarını, gebelik oranını olumsuz etkilemeden, azalttığı gösterilmiştir (Biljan vd., 1998). Alternatif olarak, siklusun başında over kistlerinin oluşumunu azalttığı gösterildiği için progestojen ön tedavisi de kullanılabilir.(Engmann vd., 1999). Ön tedavi verilmesi planlanırsa, rejimin seçimi ovaryan stimülasyon protokolüne ve hasta gruplarına göre değişir.

GnRH agonist protokolü

KOK'lar stimülasyondan önceki siklusun 2. veya 3. gününden itibaren başlatılabilir ve en az 3 hafta boyunca devam ettirilebilir.

Kısa GnRH agonist protokolünde, agonist ilaç, 14 veya daha fazla günlük KOK kullanımından sonra başlatılabilir. (KOK ön tedavisinin son haftasıyla örtüşür).

GnRH antagonist protokolü

KOK haplar, bir önceki siklusun 2. veya 3. gününden başlayarak 2 ila 3 hafta boyunca verilebilir. KOK hapların kesilmesini takip eden 5 günlük bir ilaçsız dönemden sonra, overyan stimülasyon siklus başlangıcının 2. veya 3. gününde başlatılabilir.(Montoya-Botero vd., 2020). Düşük yanıt olarak kabul edilen kadınlarda(Patrizio vd., 2015), luteal faz östradiol ön tedavisi tercih edilebilir, önceki döngünün 20. gününde başlar ve adet başlangıcının 2. gününde kesilir, 2. veya 3. günlerde başlayan

gonadotropin kullanımı ile ovaryan stimülasyona devam edilir.(Cindy Farquhar vd., 2017).

1.KOK haplarla ön tedavi

Agonist sikluslarda KOK ile ön tedavi uygulanması ile uygulanmamasının canlı doğum veya devam eden gebelik oranında anlamlı bir farka yol açmadığı gösterilmiştir.(Cindy Farquhar vd., 2017). Antagonist protokollerde ise KOK ile ön tedavi uygulanması, ön tedavi uygulanmamasına kıyasla daha düşük canlı doğum veya devam eden gebelik oranıyla ilişkilidir. Bu durumun olası bir açıklaması overyan stimülasyon döngüsü sırasında endometriyal reseptivitenin değişmesidir. Bu durumda, KOK ön tedavisi uygulanan antagonist sikluslarda üretilen embriyoların dondurulması, çözülmesi ve sonraki bir siklusta transfer edilmesi düşünülebilinir.

2.Progestojen ön tedavisi

Progestojen ön tedavisi uygulanmasını ve uygulanmamasını karşılaştıran randomize kontrollü çalışmalar (RKÇ) arasında, canlı doğum veya devam eden gebelik oranında anlamlı bir fark gösterilememiştir. Bununla birlikte, agonist sikluslarda progestojen ön tedavisinin kullanılması daha düşük over kisti oluşumu insidansı ile ilişkilidir.(Cindy Farquhar vd., 2017)

3.Östrojen ön tedavisi

Benzer şekilde, östrojen ön tedavisi ile ön tedavi uygulanmamasını karşılaştıran RKÇ'ler arasında, canlı doğum veya devam eden gebelik oranında anlamlı bir fark gösterilememiştir. (Cindy Farquhar vd., 2017) Luteal faz östrojen ön tedavisinin, düşük ovaryan yanıtı olan hastalarda oosit verimini ve klinik sonuçları iyileştirebileceği, bunu da FSH salgılanmasını inhibe ederek, luteal

folikülün geçiş döneminde, kontrollü ovaryan hiperstimülasyon sırasında foliküler büyümenin senkronizasyonunu teşvik edeceği ve FSH-duyarlı foliküllerin asenkron gelişimini önleyebileceği öne sürülmüştür. (Ye vd., 2009). 552 hastayı içeren kör olmayan RKÇ'de oosit veriminde ve klinik gebelik oranında herhangi bir fark gösterilmemiştir .(S. Zhang vd., 2022).

4.Endometriozisli hastalarda ön tedavi

Daha önceki çalışmalarda endometriozisli kadınlarda GnRH agonist ön tedavisi ile sonuçlarda iyileşme gösterilmiştir. IVF veya intrasitoplazmik sperm enjeksiyonu (ICSI) öncesinde uzun süreli GnRH agonist tedavisi uygulanmasının endometriozisli kadınlarda gebelik oranlarını iyileştirdiği öne sürülmüştür.(Marcus & Edwards, 1994; Nakamura vd., 1992). GnRH agonist protokolü ile kümülatif canlı doğum oranı, klinik gebelik oranı ve ovaryan stimülasyonunu takiben toplanan oosit sayısı üzerinde önemli bir pozitif etki gösterilmiştir. (Sallam vd., 2006). Bununla birlikte, sonraki çalışmalar mevcut kanıtların niteliğini ve uzun süreli GnRH agonist tedavisinin etkinliğine ilişkin bulguları sorgulamıştır.(Kaponis vd., 2020) (Rodríguez-Tárrega vd., 2020). 2019'da yayınlanan ve 5 ek çalışmayı da içeren en güncel Cochrane derlemesinde (Georgiou vd., 2019), uzun süreli GnRH agonist tedavisinin endometriozisli kadınlarda üreme sonuçlarını iyileştirip iyileştirmediğini belirlemek için yeterli kanıt olmadığı sonucuna varılmıştır. Uzun süreli GnRH agonist tedavisinin IVF ve ICSI sonrası sonuçlar üzerindeki etkisini belirlemek için kanıt düzeyi yüksek yeni çalışmalarla değerlendirilmesi gerekmektedir.

Overyan yanıtı zayıf olan hastalar gibi seçilmiş hasta gruplarında, siklus zamanlaması, senkronize foliküler gelişim ve

over kisti oluşumunun azaltılması gibi durumlarda ön tedavi yararlı olabilir.

Overyan stimülasyonunun genel stratejisi

Genel olarak, istenen biyolojik etkiyi elde etmek için bir ilacın en düşük dozunun kullanılması gerektiği kabul edilir. İlk siklusta, çoğu klinisyen ihtiyatlılık ilkesini uygulayacak, diğer belirteçlerin ve hastanın önceki tedavilerine ilişkin bilgilerle birlikte en düşük etkili stimülasyon dozuyla başlayacaktır. Bununla birlikte, tedavi döngüsü ilerledikçe, klinisyen hastanın yanıtına göre overyan stimülasyon ilaçlarının dozunu ayarlayabilir ve böylece daha bireyselleştirilmiş bir tedavi yaklaşımı sağlamış olur.

Over yanıtının öngörülmesi

Overyan yanıt, stimülasyondan sonra overde gelişen antral folikül ve oosit sayısı ile tanımlanır ve bu da doğrudan over rezervi ile ilişkilidir. Overyan stimülasyona verdikleri yanıta göre üç grup tanımlanmış ve bunlar normal, yüksek ve zayıf yanıt verenler olarak gruplandırılmıştır.(The ESHRE Guideline Group on Ovarian Stimulation vd., 2020).Bu hastaları optimum şekilde yönetmek için farklı stratejiler geliştirilmiştir. Overyan yanıt; hasta özellikleri, klinik tanı ve bazal anti-Müllerian hormon (AMH), FSH, LH ve östradiol (E2) gibi laboratuvar belirteçleri ile tahmin edilebilir. Bununla birlikte, bu belirteçler çok hassas değildir ve sonucu tahmin etmek her zaman mümkün değildir. Önceki overyan stimülasyona yanıt, over yanıtının en iyi belirleyicisi olmaya devam etmektedir.

Normal yanıt veren kadınlar, overyan stimülasyonunu takiben optimal yumurtalık yanıtına (10-15 oosit arasında) sahip kadınları ifade eder. (Sunkara vd., 2011). Yüksek yanıt veren kadınlar, gonadotropin uygulamasına aşırı yanıt ve OHSS için artmış

risk ile karakterize edilir. Yüksek yanıt öyküsü veya yüksek sayıda toplanan oosit (> 15 oosit), PKOS, yüksek AMH (≥ 25 pmol/L veya 3.5 ng/mL), yüksek antral folikül sayısı (AFC) değerleri (siklusun 3. gününde transvajinal ultrasonla ölçülen 2- 10 mm'lik> 16 folikül) veya düşük FSH değerleri (≤4 IU/L) yüksek ovaryan yanıtın göstergeleri olarak kabul edilir. (O'Flynn, 2014) (The ESHRE Guideline Group on Ovarian Stimulation vd., 2020)

Overyan stimülasyona düşük overyan yanıt, foliküler yanıtta azalma olduğunu gösterir ve toplanan oosit sayısının azalması ile sonuçlanır. 2013'te yayınlanan NICE (National Health and Institute Clinical Excellence) kılavuzuna göre, düşük over yanıtı; düşük toplam antral folikül sayısı (≤ 4), AMH (≤5.4 pmol/L veya 0.75 ng/mL) veya yüksek FSH değerleri (>8.9 IU/L) ile tahmin edilebilir (O'Flynn, 2014).

Bologna kriterlerine göre, Kötü Over Yanıtı (POR) aşağıdaki kriterlerden en az ikisinin mevcut olduğu bir durum olarak tanımlanmaktadır:

(i) İleri kadın yaşı > 40 yaş,

(ii) Önceki stimülasyona zayıf yanıt (Standart bir overyan stimülasyondan sonra toplanan ≤ 3 oosit)

(iii) Anormal over rezerv testi (AFC <5-7 folikül ve/veya AMH <1.1 ng/mL) (Ferraretti vd., 2011)

2016 yılında POSEIDON (Patient Oriented Strategies Encompassing Individualized Oocyte Number) grubu olarak bilinen başka sınıflandırma tanıtılmıştır. (Alviggi vd., 2016).

Hastalar:

(i) Yaş

(ii) Over rezervi belirteçleri

(iii) Bu bilgi mevcutsa, önceki ovaryan stimülasyon döngüsündeki over yanıtına (toplanan oosit sayısı) göre 4 alt gruba ayırmıştır.

POSEIDON sınıflandırması, kötü over yanıtlı hastaları 'beklenmeyen POR' (Grup 1 ve 2) ve 'beklenen POR' (Grup 3 ve 4) olmak üzere iki ana kategoriye ayırır.

Grup 1, 35 yaşın altında olup yeterli over rezervine (AFC ≥5 veya AMH ≥1.2 ng/mL) sahip olan ve ovaryan stimülasyondan sonra beklenmedik zayıf over yanıtı (<4 oosit toplanan hastalar alt grup 1a'ya aittir) veya suboptimal (4-9 oosit toplanan hastalar alt grup 1b'ye aittir) veren hastaları ifade eder.

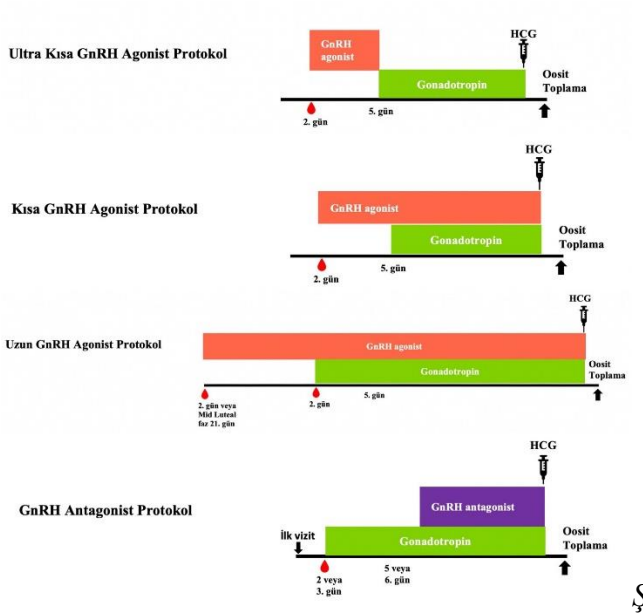
Grup 2, yeterli over rezerv parametrelerine (AFC ≥5 veya AMH ≥1.2 ng/mL) sahip, beklenmedik zayıf (<4 oosit toplanan hastalar alt grup 2a'ya aittir) veya suboptimal (4-9 oosit toplanan hastalar alt grup 2b'ye aittir) over yanıtı ile başvuran 35 yaş ve üzeri hastaları ifade eder.

Grup 3, zayıf over rezerv belirteçleri (AFC <5 veya AMH <1.2 ng/mL) olan 35 yaş altı hastaları ifade eder.

Grup 4, zayıf over rezerv belirteçleri (AFC <5 veya AMH <1.2 ng/mL) olan 35 yaş ve üzeri hastaları ifade eder. POSEIDON kriterleri, ART tedavisi gören eksojen gonadotropinlere 'beklenen' veya 'beklenmeyen' kötü over yanıtı olan hastaların üreme potansiyelini daha iyi yansıtmaktadır.

Overyan stimülasyon protokolleri

IVF tedavisi gören hastaların kontrollü ovaryan stimülasyonu (KOS) için yıllar içinde çeşitli stimülasyon protokolleri ortaya çıkmıştır. Bu protokollerin iyileştirilmesi, klinik uygulamada kademeli değişikliklere yol açmış ve yeni protokollerin eklenmesi, farklı hasta gruplarına uygun mevcut seçeneklerini artırmıştır.



Şekil 1. In-vitro fertilizasyonda (IVF) kullanılan çeşitli stimülasyon protokolleri.

GnRH: gonadotropin salgılatıcı hormon.

Kaynak: Patricia N. P. Ip, Jennifer S. M. Mak, Tracy S. M. Law, Karen Ng & Jacqueline

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1.GnRH agonist protokolü

Klinik uygulamada kullanılan üç GnRH agonist protokolü vardır; uzun, kısa ve ultra kısa agonist protokolleri (Şekil 1). Ancak önceden popüler olan bu protokoller günümüzde daha az kullanılmaktadır. Enjeksiyon (deslorelin, goserelin, leuprorelin ve triptorelin) veya burun spreyi (nafarelin) yoluyla uygulanabilen çeşitli GnRH agonist preparatları vardır. Hipofiz-over aksını down regüle etmek için GnRH agonistinin bir süre uygulanmasıyla başlar, sonrasında overleri uyarmak için gonadotropinlerin uygulanması ile devam eder.

Uzun GnRH agonist protokolü, stimülasyona başlamadan en az 2 hafta önce GnRH agonistinin uygulanmasıyla başlar ve genellikle menstrüel siklusun 2. gününden (uzun foliküler protokol) veya önceki siklusun orta luteal fazından (21. gün) itibaren uygulanır (uzun luteal protokol). Üç veya daha fazla folikül 16-18 mm boyutuna ulaştığında insan koryonik gonadotropin (hCG) trigger enjeksiyonu yapılır, GnRH agonisti ve gonadotropin uygulamasına trigger gününe kadar devam edilir. (Siristatidis vd., 2015) Kısa GnRH agonist protokolünde, GnRH agonisti menstrual siklusun 2. gününden itibaren uygulanmakta, bu da başlangıçta bir 'alevlenme etkisi' yaratmakta ve hCG uygulamasına kadar devam etmektedir. Günlük gonadotropin enjeksiyonlarına GnRH agonisti uygulanmasından 2-3 gün sonra başlanır. (Garcia vd., 1990) Ultra kısa GnRH agonist protokolü, GnRH agonistinin adet döngüsünün 2. gününden itibaren 3 gün boyunca uygulanmasını ve yalnızca alevlenme etkisinin kullanılmasını sağlar.(Siristatidis vd., 2015). Toplam 844 siklusu içeren bir meta-analizde, gebelik oranları kısa ve uzun agonist protokolleri arasında benzer bulunmuştur (Hughes vd., 1992) Daha sonra yayınlanan ve 5662 siklusu içeren bir derlemede hastalar dört yaş aralığına ayrılmıştır: <31 yaş, 31-35 yaş,

36-40 yaş ve >40 yaş. Uzun agonist protokolü, hasta yaşından bağımsız olarak kısa agonist grubuna kıyasla toplanan oosit sayısında anlamlı bir artış, daha kaliteli embriyolar ve daha yüksek klinik gebelik oranı ile ilişkilendirilmiştir. (Ou vd., 2015).

Bununla birlikte, uzun protokolde kullanılan toplam gonadotropin dozu daha yüksek ve stimülasyon süresi daha uzundur. Başka bir RKÇ'de, toplanan oosit sayısı kısa agonist protokolünde önemli ölçüde daha az olmuştur.(Sunkara vd., 2014). Uzun GnRH agonist protokolünde daha uzun stimülasyon süresi (Devroey vd., 2008; Gun Eryilmaz vd., 2012) olduğuna dikkat etmek önemlidir. Genel olarak, uzun GnRH agonist protokolü, hastanın yaşından bağımsız olarak, toplanan oosit sayısı, implantasyon ve gebelik oranları açısından kısa GnRH agonist protokolünden daha üstün görünmektedir. Kısa GnRH agonist protokolü ise, GnRH agonistinin ilk alevlenme etkisinden faydalanılan ve uzun protokolle ilişkili aşırı hipofiz baskılanmasından kaçınmak isteyen kötü over yanıtlı hastalar için alternatif bir protokoldür.

2.GnRH antagonist protokolü

Son yıllarda, GnRH antagonist protokolü basitliği, güvenliği ve etkinliği nedeniyle kontrollü over stimulasyon için popülerlik kazanmıştır. IVF tedavisi için overyan stimülasyon uygulanan hastaların çoğunda tercih edilen protokol olarak agonist protokolün yerini almıştır. Bu protokolde gonadotropinlere adet döngüsünün 2. veya 3. gününde başlanır, folikülün büyüklüğüne bakılmaksızın (sabit-fixed protokol) 5. veya 6. günden itibaren veya öncü folikül 12-14 mm'ye ulaştığında (flexible-esnek yaklaşım) GnRH antagonisti eklenir (Şekil 1). GnRH antagonisti protokolünün, normal ve yüksek yanıt öngörülen kadınlar için ilk seçenek olduğu

artık yaygın olarak kabul edilmektedir. Bu tercih, öncelikle OHSS riskini en aza indirmeyi amaçlamaktadır.(The ESHRE Guideline Group on Ovarian Stimulation vd., 2020)

3.GnRH agonist ve GnRH antagonist protokolleri arasında karşılaştırma

Eskiden popüler bir tedavi protokolü olan uzun GnRH agonist protokolü artık ikinci basamak bir seçenek olarak kabul edilmektedir. Çünkü şu an tercih edilen protokol olan antagonist protokolünün benzer bir kümülatif canlı doğum oranı ile daha düşük OHSS riski(Al-Inany vd., 2016; Wang vd., 2017) ve daha düşük siklus iptali insidansıyla (Al-Inany vd., 2016) sonuçlandığı gösterilmiştir. Ayrıca antagonist protokol, uzun GnRH agonist protokolüne kıyasla daha kısa tedavi süresi ve daha az miktarda gonadotropin kullanımı ile ilişkilidir.(J. A. F. Huirne vd., 2004; Yang vd., 2021; W. Zhang vd., 2020).Antagonist protokol normal veya yüksek yanıt veren kadınlarda ilk tercih edilen protokol olsa da düşük yanıt veren kadınlarda protokol seçimi tartışmalı olmaya devam etmektedir.

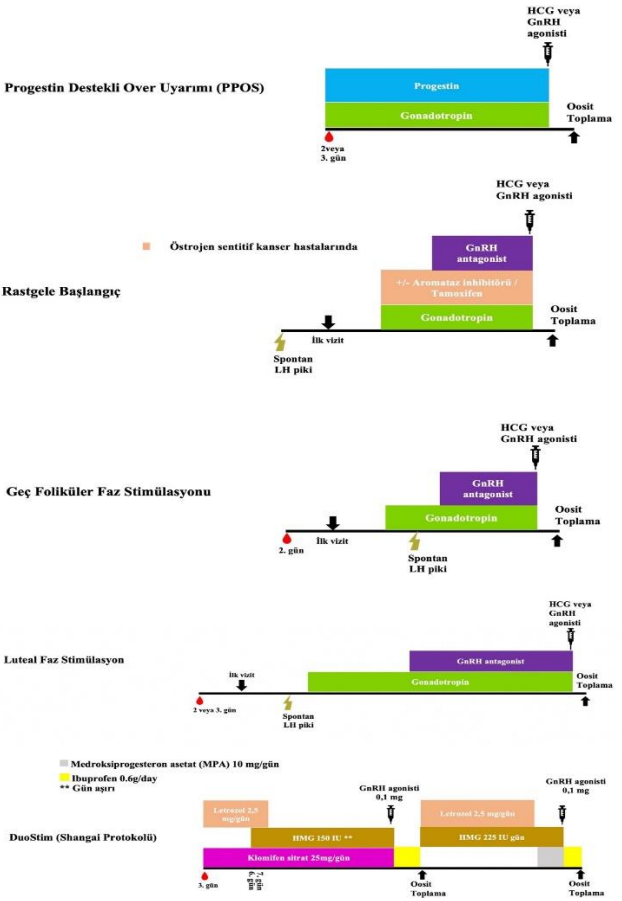
Daha önce yapılan birkaç çalışmada kötü over yanıtlı hastalarda kısa GnRH agonist protokolü ile GnRH antagonist protokolü karşılaştırılmış ve kısa GnRH agonist protokolü uygulananlarda antagonist protokollere kıyasla daha yüksek ortalama olgun oosit sayısı ve daha yüksek implantasyon oranı bildirilmiştir.(Akman vd., 2001; Demirol & Gurgan, 2009; Malmusi vd., 2005). Ancak, daha sonra yapılan birkaç çalışmada kötü over yanıtlı hastalarda iki protokol arasında anlamlı bir fark bulunamamıştır(Berin vd., 2010; Devesa vd., 2010; Kahraman vd., 2009; Schmidt vd., 2005). Buna ek olarak yapılan bir RKÇ'de esnek

GnRH antagonisti protokolünün kötü over yanıtlı hastalarda GnRH agonisti protokolüne kıyasla anlamlı derecede daha yüksek devam eden gebelik oranlarıyla ilişkili olduğunu öne sürülmüştür.(T. G. Lainas vd., 2008). Kötü over yanıtlı kadınlarda antagonist protokol veya kısa agonist protokol kullanımı arasındaki seçim bireysel bir tercih olmaya devam etmektedir.

4.Progestin destekli over uyarımı

Progestin destekli over stimülasyonu (PPOS) protokolü Kuang ve arkadaşları (2015) tarafından geliştirilmiştir (Şekil 2). Kontrollü over stimulasyonunda GnRH agonisti veya antagonisti kullanmak yerine LH pikini engellemek için progestinin negatif geri bildirimin kullanıldığı yeni bir protokolüdür. Guan ve arkadaşları (2021) tarafından PPOS üzerine yapılan yeni bir meta-analizde, toplam 1.885 kadın (PPOS protokolünde 942 kadın ve kontrol grubunda 943 kadın) incelenmiştir.(Guan vd., 2021) Meta-analiz, Ocak 2015 ile Kasım 2020 arasında PPOS üzerine yapılan ve beş antagonist protokolü çalışmasını, iki kısa protokol çalışmasını, bir uzun GnRH agonist protokolü çalışmasını ve bir doğal siklus çalışmasını içeren RKÇ'leri içermektedir. PPOS grubu ile kontrol grubu arasında klinik, devam eden gebelik ve kümülatif canlı doğum oranı açısından anlamlı bir fark olmadığını göstermiştir. PPOS protokolü, progestojenin oral yoldan uygulanabilmesi ve antagonistten daha ucuz olması avantajına sahiptir. Bununla birlikte, dezavantajı endometrium üzerindeki olumsuz etkisidir ve bu da onu taze embriyo transferi için uygunsuz hale getirmektedir. Öte yandan, aynı menstrüel döngüde preimplantasyon genetik testi (PGT), fertilite preservasyonu, donör döngüleri veya aynı döngüde çift stimülasyon geçirenler gibi elektif dondurma politikası planlandığında tercih edilen bir alternatif olabilir. PPOS

protokolünde yaygın olarak kullanılan bazı progestinler arasında medroksiprogesteron asetat 10 mg/gün, didrogesteron 20 mg/gün veya mikronize progesteron (UtrogestanVR) 200 mg/gün bulunmaktadır. Progestinler Gonadotropin stimülasyonu ile birlikte başlanır ve LH seviyesi de dahil olmak üzere ovülasyon tetikleme gününe kadar devam edilir. LH yeterince baskılanmazsa, progestin dozu artırılabilir veya bir antagonist eklenebilir.



*Şekil 2. In-vitro fertilizasyonda (IVF) kullanılan çeşitli stimülasyon protokolleri. GnRH: gonadotropin salgılatıcı hormon; LH: lüteinizan hormon; hMG: insan menopozal gonadotropini; **: gün aşırı.*

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Over stimülasyonunda gonadotropin seçimi

Folikül gelişimini uyarmak için kullanılan FSH, LH ve hCG gibi çeşitli gonadotropin preparatları vardır.

1.FSH hazırlığı

FSH, ön hipofiz bezi tarafından salgılanan glikozillenmiş bir proteindir. Hem idrar kaynaklı FSH (u-FSH) hem de rekombinant FSH (r-FSH) over stimülasyonu için kullanılabilir. U-FSH 1970'lerde kullanılan ilk nesil gonadotropinlerdir ve menopoz dönemindeki kadınların idrarından elde edilir. Saflaştırılmış FSH ve yüksek oranda saflaştırılmış FSH gibi daha rafine idrar preparatları 1980'lerden beri üretilmektedir. Öte yandan, r-FSH, rekombinant DNA teknolojisi kullanılarak üretilen yeni nesil gonadotropinlerdir.(Out vd., 1997). r-FSH, üretimi idrar toplanmasına bağlı olmadığından, u-FSH ile karşılaştırıldığında üründen ürüne minimum farklılıkla daha yüksek düzeyde saflık ve biyokullanılabilirlik ile karakterize edilir. r-FSH'nin düşük immünojenitesi de gonadotropinlerin deri altından uygulanmasına olanak sağlamaktadır.(Bergh, 1999). Günümüzde hem insan menopozal gonadotropinleri (hMG) hem de r-FSH yaygın olarak kullanılmaktadır.

2.Over stimülasyonu için rekombinant FSH ve üriner FSH

Geleneksel IVF ve ICSI döngülerine giren kadınlarda over stimülasyonu için u-FSH v e r-FSH'nin etkinliğini ve güvenliğini karşılaştırmak için çeşitli RKÇ'ler ve meta-analizler yapılmıştır. Önceden yapılan bir sistematik derlemede u-FSH kullanılarak siklus başına daha yüksek bir klinik gebelik oranı bildirilmiştir (Daya vd., 1995). Bununla birlikte, Cochrane derlemeleri ve meta-analizleri dahil olmak üzere yayınlanmış literatürden elde edilen daha güncel

kanıtlar, IVF/ICSI uygulanan kadınlarda u-FSH ve r-FSH arasında oosit ve embriyo kalitesi, kümülatif canlı doğum oranı veya OHSS riski açısından anlamlı bir fark olmadığını göstermiştir. (Al-Inany vd., 2003; Al-Inany vd., 2008; Van Wely vd., 2011).

Öte yandan, saflaştırılmış u-FSH'nin uzun GnRH agonist protokolü uygulanan ileri yaş kadınlarda r-FSH'den daha etkili olduğu gösterilmiştir. (Mohamed vd., 2006). Çin'de yapılan 508 kadını içeren prospektif, randomize bir çalışmada IVF/ICSI uygulanan 37 yaş üstü kadınlarda, u-FSH ile tedavi edilenler, r-FSH ile tedavi edilenlerle karşılaştırıldığında u-FSH kullanımında, anlamlı derecede daha yüksek iki pronükleuslu zigot oranı, daha yüksek Grade I embriyo oranı, hCG gününde daha yüksek endometriyal kalınlık ve daha düşük transfer edilemeyen embriyo oranı bulunmuştur. (Liu vd., 2015).Ayrıca r-FSH, u-FSH'ye kıyasla daha yüksek bir maliyetle ilişkilendirilmektedir. Genel olarak, gonadotropin stimülasyonuna normal yanıt vermesi beklenen hastalarda, u-FSH ve r-FSH arasında sonuçlarda çok az fark var gibi görünmektedir, bu nedenle seçim klinisyenlere bağlıdır.

3.Over stimülasyonunda LH ile birlikte tedavi

Ekzojen FSH, granüloza hücre proliferasyonunu ve foliküler büyümeyi uyarırken; LH teka hücrelerinde androjen üretimini teşvik eder ve bu androjen daha sonra aromatizasyon yoluyla granüloza hücreleri tarafından östrojene dönüştürülür. Ayrıca LH, foliküler büyüme ve oosit olgunlaşması için de çok önemlidir. LH ve FSH eksikliği, ileri anne yaşına sahip, iyatrojenik GnRH eksikliği olan ve kötü over yanıtlı hastalarda over stimülasyonuna karşı düşük yanıtı açıklayabilir. Geleneksel olarak LH aktivitesi, idrar gonadotropin preparatlarında bulunan LH'nin uygulanmasıyla veya onun yerine

hCG'nin kullanılmasıyla sağlanabilir. Daha yakın zamanlarda, rekombinant LH (rLH) kullanılabilir hale gelmiştir. Klinik uygulamada hMG ve rLH, LH'nin piyasada bulunan iki yaygın kaynağıdır.

Hipogonadotropik hipogonadizmi olan kadınlarda optimal klinik sonuçlar FSH ve LH kombinasyonu ile elde edilir. Bu, (1) u-FSH (hem FSH hem de LH içerir) veya (2) r-FSH ile eksojen hCG kombinasyonu veya (3) r-FSH ile rLH kombinasyonu uygulanarak gerçekleştirilebilir. ("Use of Exogenous Gonadotropins in Anovulatory Women", 2008)

Yakın tarihli bir metaanalizde Conforti ve arkadaşları (2021), r-FSH ve rLH ortak tedavisinin, over stimülasyonu uygulanan 35 ila 40 yaş arasındaki kadınlarda klinik gebelik ve implantasyon oranlarını iyileştirdiğini öne sürmüştür. (Conforti vd., 2021) YÜT sırasında r-FSH'ye rLH eklenmesinin kötü over yanıtlı hastalarda faydalı etkileri olabileceğini gösteren çalışmalar da vardır. Bu kombinasyon FSH reseptörünün ekspresyonunun artmasına, dolayısıyla foliküler büyümeyi artırmakta ve granüloza hücresi apoptoz oranını azaltmaktadır(Bosch vd., 2011; Hill vd., 2012; Humaidan vd., 2017; Lehert vd., 2014)

Bununla birlikte, uzun GnRH agonist protokolünde ESHRE Bologna kriterlerine göre kötü over yanıtlı hastaları içeren büyük bir RKÇ'de (n=939), tedavide rLH eklenen hastalardan elde edilen oosit sayısında anlamlı bir fark bulunmamıştır. Ancak, orta ve şiddetli kötü over yanıtlı hastalar için daha yüksek bir kümülatif canlı doğum oranı(Humaidan vd., 2017) saptanmıştır. Buna ek olarak, 2018'de yayınlanan bir sistematik inceleme, rLH takviyesinin faydasının yalnızca beklenmeyen 36-39 yaş arası kötü over yanıtlı kadınlarda

belirgin olduğu, kötü over yanıt veren diğer yaş gruplarında kullanımının ise tartışmalı olduğu sonucuna varmıştır. (Alviggi vd., 2018)

Çeşitli çalışmalarda farklı LH kaynaklarının etkisi değerlendirilmiştir. GnRH antagonisti protokolü uygulanan zayıf ovaryen yanıt verenlerde rLH ve hCG eklenmesinin etkisini karşılaştıran çift kör randomize bir çalışmada, siklus iptal oranları, toplanan oosit sayısı, döllenme oranları, elde edilen embriyo sayısı, implantasyon, klinik gebelik ve canlı doğum oranlarında anlamlı bir fark bulunmamıştır.(Mak vd., 2017) .Diğer çalışmalar da üriner LH içeren hMG ve rLH arasında toplam ve günlük gonadotropin dozu, klinik gebelik ve canlı doğum oranları açısından önemli bir fark olmadığını bildirmiştir.(Trew vd., 2010; Van Wely vd., 2011). Bununla birlikte, rLH grubunda toplanan oosit sayısı hMG grubundan önemli ölçüde daha yüksektir. KOS protokolleri sırasında farklı LH preparatlarının döngü karakteristikleri ve sonuçları üzerindeki etkisini değerlendiren daha yeni bir literatür taraması da hMG ile r-FSH'ye r-LH eklenmesi arasında anlamlı bir fark olmadığı sonucuna varmıştır.(Orvieto, 2019). Ayrıca, rLH uygulamasının dozu ve zamanlaması konusunda hala tartışmalar devam etmektedir. Stimülasyonun başlangıcından itibaren uygulanan r-FSH'nin rLH'ye oranın 2:1 olması, 36-40 yaş arası kadınlarda daha iyi bir implantasyon oranı sağlamak için yeterli görünmektedir.(Behre vd., 2015; Bosch vd., 2011). rLH uygulamasının zamanlamasıyla ilgili olarak, bazı yazarlar LH'nin ovaryan stimülasyonun başlangıcında başlatılmasını önerirken(Behre vd., 2015; Bosch vd., 2011), diğerleri ovaryan stimülasyonun ara aşamasından itibaren LH eklenmesini önermiştir.(Konig vd., 2013; Vuong vd., 2015). Bu konuda kesin bir fikir birliği yoktur. Her halükârda, stimülasyon protokolüne LH

eklenmesi ihtiyacını belirlemek için ovaryan stimülasyonun başında ve sırasında serum LH seviyelerini, özellikle de beklenmeyen şekilde yavaş foliküler gelişim izlenen hastalarda izlemek mantıklı görünmektedir. (Eftekhar & Tabibnejad, 2021)

Gonadotropin dozunun seçilmesi

Başlangıç gonadotropin dozu, öngörülen yanıta göre bireyselleştirilmelidir. Geleneksel olarak yüksek yanıt öngörülen kadınlarda çoğu hekim günlük 100-150 ünite FSH gibi düşük bir dozla başlar. Buna karşılık, düşük yanıt öngörülen kadınlarda, 300 ünite FSH civarında daha yüksek bir günlük doz kullanılır. Önceden tahmin edilen normal yanıtı olan kadınların başlangıç dozu genellikle 150 ile 300 ünite FSH arasındadır. Folikül stimülasyonu için dozajın bireyselleştirilmesi, normal düzeyde bir yanıt olasılığını ve bu sayede gebelik ve canlı doğum olasılığını artırır. Bununla birlikte, optimal sayıda oosit elde etmek için uygun FSH dozunun belirlenmesi klinisyenler için bir zorluk teşkil etmektedir, çünkü yetersiz stimülasyonun suboptimal klinik sonuca yol açma riskini, hiperstimülasyon riskini ve maliyet etkinliğini dengelemeleri gerekmektedir. Önceki sistematik incelemeler hem AFC hem de AMH'nin over stimulasyonuna yanıtını tahmin etmede bazal FSH'den üstün olduğunu göstermiştir.(Broekmans vd., 2006; Broer vd., 2009).

Moolenaar ve arkadaşları (2011) Markov karar-analitik modelini önermiş ve IVF tedavisi için uygun olan kadınlarda FSH dozunun over rezervine göre bireyselleştirilmesinin maliyet-etkin olabileceğini göstermiştir.(Moolenaar vd., 2011) OPTIMIST çalışması, IVF tedavisinin maliyet etkinliğini optimize etmek için bireyselleştirilmiş FSH stimülasyon dozajları hipotezini

değerlendirmiştir (Van Tilborg vd., 2017). Çalışmada, AFC tabanlı bireyselleştirilmiş FSH dozu (günde 100-450 IU) ile standart doz (günde 150 IU) arasında ilk döngüde veya kümülatif canlı doğum oranında anlamlı bir fark bulunmazken, bireyselleştirilmiş doz stratejisi daha yüksek bir maliyete neden olmuştur. Yazarlar, bir bütün olarak IVF/ICSI popülasyonu için bireyselleştirilmiş FSH dozajlamasının canlı doğum oranlarını iyileştirmediği ve maliyetleri artırdığı için devam edilmemesi gerektiği sonucuna varmıştır. IVF/ICSI için planlanan düzenli adet döngüsü olan kadınlar için günde 150 IU'luk bir standart FSH başlangıç dozu önerilmektedir. (Van Tilborg vd., 2017). Başka bir randomize kontrollü çalışmada da FSH dozunun artırılmasının yalnızca daha fazla sayıda oositle sonuçlandığını ancak daha fazla canlı doğumla sonuçlanmadığını göstermiştir (Arce vd., 2014)Yüksek yanıt veren kadınlar genellikle yüksek AFC ve yüksek AMH seviyesi ile karakterize edilir ve PCOS bunun iyi bilinen bir örneğidir. Bu kadınlar OHSS geliştirmeye yatkındır. Bu grupta metformin yaygın olarak OHSS insidansını düşürmesi nedeni ile kullanılmıştır. Bununla birlikte, metformin antagonist protokolle birlikte kullanıldığında, kümülatif canlı doğum oranı azalabilir.(Tso vd., 2020) Öte yandan, uzun agonist protokolü kullanıldığında kümülatif canlı doğum oranında herhangi bir azalma olmamıştır. Yüksek yanıt veren kadınlarda KOK haplar ile ön tedavi de yaygın olarak kullanılmaktadır, çünkü retrospektif olarak yapılan bir çalışmada gebelik sonuçlarının iyileştiği gösterilmiştir. (Pan vd., 2015)

Agonistlerin ovulasyonu tetiklemesi nedeni ile yüksek yanıt öngörülen kadınlarda, GnRH antagonist protokolü OHSS riskini azalttığından dolayı önerilmektedir.(The ESHRE Guideline Group on Ovarian Stimulation vd., 2020) (Youssef vd., 2014) Bununla

birlikte, GnRH agonist protokolleri kullanılacaksa, OHSS riskini azaltmak için azaltılmış bir gonadotropin dozu önerilmektedir.(Oudshoorn vd., 2017)

Kötü over yanıtlı hastalar ve zayıf yanıt veren kadınlar yeterince güçlü klinik çalışmaların olmaması nedeniyle yardımcı üreme teknolojilerinde bir zorluk olmaya devam etmektedir. Bir dizi strateji önerilmiş olsa da bu hasta grubu için en uygun overyan stimülasyon protokolü konusunda henüz kesin bir fikir birliği yoktur.

Preovulatuar progesteron artışı

IVF uygulanan kadınlarda serum progesteron seviyesinde genellikle over stimülasyonunun sonundaki geç foliküler faz sırasında hCG uygulamasının yapıldığı gün artış gözlenir. Progesteronun bu preovulatuar yükselişi, erken luteinizasyonun bir sonucu olarak ortaya çıkar.(Venetis vd., 2007). KOS protokollerinde GnRH analoglarının kullanılmasıyla erken luteinleşme önlenebilir. Bununla birlikte, hipofiz down regülasyonuna rağmen uyarılmış IVF sikluslarının %12.4-52.3'ünde preovulatuar progesteron artışı meydana gelebilir.(Venetis vd., 2007) Preovulatuar progesteron artışının IVF sonuçları üzerindeki etkisi, progesteron ölçüm yönteminin ve eşik değerlerinin heterojenliği nedeniyle tartışmalı olmaya devam etmektedir. Bazı çalışmalar, serum progesteron seviyeleri yükseldiği durumlarda endometriyal reseptivite ve klinik sonuçlar üzerinde olumsuz bir etki olduğunu bildirmiştir.(Bosch vd., 2010; Yovich vd., 2015).

Bu gibi durumlarda sonraki siklusta normal endometriyal reseptivite geri kazanılınca, embriyo transferine olanak tanıyan freze-all stratejisi kullanılabilir. Öte yandan, uyarılmış IVF

döngülerinde preovulatuar progesteron artışı, aşırı uyarımdan ve hCG tetikleyicisinin uygulanmasında gecikmeden kaçınarak önlenebilir.

Ovulasyon tetiklenmesi

Ovulasyon tetiklenmesi, kontrollü over stimulasyonundaki kilit prosedürlerden biridir ve foliküller uygun bir boyuta ulaştığında oosit alımına hazırlık için oositlerin olgunlaşmasını kolaylaştırır. Genel olarak, oosit alım gününde 16-22 mm ye ulaşan foliküller, döllenmeye ve embriyo gelişimine yönelik yeterliliğe sahip olgun oositlerle ilişkilendirilmiştir.(Revelli vd., 2014) .Ovulasyon indüksiyonu için klomifen sitrat ve/veya hMG kullanan hastalarla yapılan çalışmalara dayanarak, ovulasyon tetiklemesi ile oosit toplanması arasındaki zaman aralığı genellikle 32-36 saattir.(Edwards & Steptoe, 1975; Testart & Frydman, 1982)

1.HCG vs GnRH agonist tetiklemesi

Geleneksel olarak, hCG her zaman ovulasyon tetikleyici ajan olarak kullanılmıştır. GnRH agonisti 1990'larda hCG'ye alternatif olarak tanıtılmıştır.(Albano vd., 1997). HCG'den daha kısa bir etki süresi ve yarılanma ömrü ile LH pikini tetikler ve bu sayede OHSS riskini azaltır.(Griesinger vd., 2007; Hernández vd., 2009; Itskovitz vd., 1991) hCG ile karşılaştırıldığında benzer oosit olgunlaşma oranı ve embriyo kalitesi elde eder.(Humaidan vd., 2011). Bununla birlikte, GnRH agonisti ile tetikleme, aynı döngüde embriyo transferi gerçekleşirse luteal faz eksikliğine ve daha kötü üreme sonuçlarına neden olabilir. (Kolibianakis vd., 2005). Embriyonun elektif kriyoprezervasyonu ve sonraki bir siklusta transfer edilmesiyle bu sorunun üstesinden gelinebilir. GnRH agonisti ile tetiklemenin yalnızca antagonist sikluslar veya PPOS uygulanan

sikluslarda kullanılabileceğini belirtmek önemlidir. GnRH agonist tetikleyicilerin etkilerini göstermeleri endojen LH piki gerektirdiğinden, agonist protokollerin hipofiz bezini halihazırda baskıladığı ve GnRH reseptörlerinin azalmasına neden olduğu için kullanımı uygun değildir.

2.Kombine hCG ve GnRH agonist tetiklemesi (Dual-trigger)

Ovulasyon tetikleyicisi olarak hCG yerine GnRH agonisti kullanıldığında, iki soruna neden olacağı bilinmektedir. Bunlar tetikleme başarısızlığı ve daha kısa yarı ömür, biyolojik etki nedeniyle luteal faz eksikliğidir. Bu nedenle bazı hekimler tetikleme başarısızlığı riskini azaltmak ve luteal faz eksikliğini önlemek için agonist ile tetiklemeye düşük doz hCG (1000-2500 IU) eklemeyi denemiş ve kullanılan düşük doz hCG'nin OHSS'ye yol açmayacağı umulmuştur.(Shapiro vd., 2011). GnRH agonisti ile tetiklemenin sadece LH değil FSH artışına da neden olduğu bilinmektedir. Haas ve arkadaşları (2020), FSH artışının, OHSS riski taşımayan normal yanıt veren kadınlarda oosit olgunlaşmasının son evresine ek bir faydası olabileceğini öne sürmüş, hCG ve GnRH tetiklemesini birleştiren ikili tetiklemenin (dual trigger) kullanımını savunmuştur. (Haas vd., 2020) Yapılan bir RKÇ'de ikili tetikleme grubunda daha yüksek sayıda oosit alındığını, daha yüksek oosit olgunlaşma oranı, blastosist oranı, klinik gebelik oranı ve kümülatif canlı doğum oranı olduğunu göstermişlerdir. (Haas vd., 2020) Yakın zamanda yapılan bir meta-analiz de çift tetikleme ile daha yüksek klinik gebelik oranı ve kümülatif canlı doğum oranı ile ilgili benzer bulgular bildirmiştir.(Hu vd., 2021). Ancak bu olumlu bulgular, özellikle normal yanıt veren kadınlarda yapılan diğer çalışmalarda doğrulanmamıştır.(Eftekhar vd., 2017; Zhou vd., 2018). Çelişkili sonuçlar göz önüne alındığında, zayıf oosit olgunlaşması öyküsü

olanlarda düşünülebilecek olsa da ikili tetikleyicinin sürekli kullanımı benimsenmemelidir.

3.Antagonist protokolde tetikleme başarısızlığı

GnRH agonisti ile tetiklenen kadınların %0.5-3.4'ünde oositlerin tamamen toplanamamasına neden olan tetikleme başarısızlığı meydana gelmektedir.(Castillo vd., 2012; Popovic-Todorovic vd., 2019); Bunun nedeni, suboptimal LH pikine sekonder olarak düşük oosit gerikazanım oranı ve yetersiz oosit maturasyonu sonucunda daha az oosit elde edilmesidir. Kadınların yaşı ve kilosunun, GnRH agonistinden sonra LH yanıtı üzerindeki ilişkisine dair çelişkili veriler mevcuttur.(Popovic-Todorovic vd., 2019). Yapılan bir çalışmada, vücut kitle indeksi (VKİ) > 25 kg/m2 olan kadınların daha zayıf bir yanıta sahip olduğunu gösterirken (G. T. Lainas vd., 2020) bir diğeri VKİ < 22 kg/m2 olan kadınlarda ise tetikleme başarısızlığı riskinin iki kat fazla olabileceğini ortaya koymuştur.(Chang vd., 2016). İki çalışmada, suboptimal yanıt verenlerde daha yüksek oranda KOK kullanımı bulunmuştur.(Meyer vd., 2015; Popovic-Todorovic vd., 2019). Dikkate değer bir diğer risk faktörü de over stimülasyonunun başlangıcında düşük LH seviyesidir. Popovic-Todorovic ve arkadaşları (2019), stimülasyon başlangıcında LH seviyesi <1.8 IU/L olanlarda %87 oranında suboptimal yanıt tespit etmiştir.(Popovic-Todorovic vd., 2019). Lu ve arkadaşları (2016) ve Chang ve arkadaşları (2016) da bazal LH seviyesinin suboptimal yanıt için en öngörücü belirteç olduğunu göstermiştir. (Chang vd., 2016; Lu vd., 2016) Meyer ve arkadaşları (2015) ovulasyon tetikleme günündeki LH seviyesinin <0.1IU/L olması durumunda %25 oranında tetikleme başarısızlığı olduğunu göstermiştir.(Meyer vd., 2015)

Son çalışmalar, farklı dozlarda GnRH agonisti (0.1-0.4 mg) uygulandığında(G. T. Lainas vd., 2019; Vuong vd., 2016) veya tekrarlanan dozlarda GnRH agonisti verildiğinde(Parneix vd., 2001) oosit veriminde herhangi bir fark bulamamıştır.

GnRH agonisti ile tetikleme, son antagonist dozu ile GnRH agonist tetiklemesi arasındaki zaman aralığına bakılmaksızın etkili bir LH pikine ve oosit olgunlaşmasına da neden olabilir. (Horowitz vd., 2020). Oosit toplama sırasında hiç oosit alınamaması hem hastalar hem de klinisyenler için oldukça stresli bir olay olabilir. Potansiyel tetikleme başarısızlığının erken tanınması ile uygun salvage yönetimi başlatılabilir ve istenmeyen sonucu tersine çevirilebilir. GnRH agonist tetiklemesinden 12 saat sonra (LH pik zamanı civarında) serum veya idrar LH seviyesinin ölçülmesi, başarılı bir tetikleme olasılığı hakkında bir ipucu sağlayabilir. (Chang vd., 2016; Cozzolino vd., 2020; Meyer vd., 2015) Çoğu çalışma, tetiklemeden 12 saat sonra LH düzeyinin <15 IU/L ve progesteronun <3 ng/mL olmasını potansiyel bir optimal yanıt için ipucu olarak kabul etmektedir. Kummer ve arkadaşları (2013) tetikleme sonrası LH seviyesi <15 IU/L olanlarda %18.8'e varan oranda boş folikül sendromu görüldüğünü bildirirken, Ganer Herman ve arkadaşları (2022) bu durumun GnRH agonist tetiklemesinden sonra kadınların toplam %2.7'sinde görüldüğünü tespit etmiştir. (Ganer Herman vd., 2022; Kummer vd., 2013) HCG ile yeniden tetikleme, tetikleme sonrası LH seviyeleri düşük olanlar için faydalı olabilir. Chang ve arkadaşları (2016) hCG ile yeniden tetikleme sonrasında tetikleme sonrası LH seviyeleri düşük olan 22 vakada başarılı oosit alımı gerçekleştirmiştir. (Chang vd., 2016)Bu grup kadınlar OHSS riski altında olduğundan, kurtarma hCG

tetiklemesinden sonra OHSS belirti ve semptomlarını değerlendirmek için yakın takip hayati önem taşımaktadır.

GnRH agonist tetiklemesini takiben, takip eden LH piki yaklaşık 28-32 saat sürer ve hem serum hem de idrar örneklerinde ölçülebilir. (Itskovitz vd., 1991).GnRH agonist tetiklemesinden sonra LH pikinin idrarda bakılması hastalar için güvenilir ve uygun bir testtir. Ayrıca, LH idrar testi, başarısız veya suboptimal bir GnRH agonisti ile tetiklemenin ardından yapılan kurtarma hCG tetiklemesinden fayda görecek hastaların belirlenmesine olanak tanır. Cozzolino ve arkadaşları (2020) tarafından gerçekleştirilen prospektif bir kohort çalışmada, LH idrar tahlili, bolus GnRH agonisti ile tetiklenen oosit donörlerinin %99'unda pozitif çıkmıştır. Bu daha sonra oosit toplanması sırasında normal bir matur oosit oranı ile sonuçlanmıştır. (Cozzolino vd., 2020) Bu nedenle, GnRH agonist tetiklemesini takiben LH pikinin idrarla test edilmesi düşünülebilir.

Tetikleme başarısızlığı olasılığını değerlendirmek için agonist tetiklemesinden yaklaşık 30 saat sonra kan veya idrar LH seviyesini veya progesteron seviyesini ölçmek mümkün olsa da tetikleme başarısızlığı veya olası tetikleme başarısızlığı olduğu tespit edilenlerin devam eden süreçteki yönetimi, oosit alımının tam zamanlaması yeniden tetikleme nedeni ile bir miktar belirsizdir ve oosit kalitesi düşebilir. Bu nedenle, bazı uygulayıcılar başarılı bir tetikleme sağlamak için agoniste az miktarda hCG eklenmesini önermektedir. Lu ve arkadaşları (2016), GnRH agonist tetikleyicisinden sonra suboptimal yanıt öyküsü olan ve sonraki sikluslarda farklı hCG dozlarında (sırasıyla 0, 1000, 2000 ve 5000 IU) kombine hCG ve GnRH agonist tetiklemesi yapılan kadınları

sonuçlarını incelemiştir. GnRH agonisti ve hCG 5000 IU grubunda orta ila şiddetli OHSS gözlenirken, diğer regimenlerin kullanıldığı gruplarda OHSS vakası görülmemiştir. Ayrıca, ikili tetikleme grupları arasında oosit toplama oranlarında önemli bir fark bulunmamıştır. Tetikleme başarısızlığını önlemek için GnRH agonisti ve düşük doz hCG (1000 IU) tetiklemesinin birleştirilmesi önerilmiştir.(Lu vd., 2016) Bununla birlikte, klinik uygulamada rutin olarak kullanılmadan önce IVF uygulanan farklı hasta gruplarında ikili tetiklemenin rolünü incelemek için daha geniş kapsamlı prospektif çalışmalara ihtiyaç vardır.

Yeni stimülasyon teknikleri

Geleneksel olarak, bir adet döngüsünde foliküler faz sırasında yalnızca tek bir antral folikül veya foliküler dalgası olduğuna inanılırdı. Bunun aksine, Baerwald ve arkadaşları (2003) düzenli adet döngüsü olan kadınların %68 inin aynı adet döngüsü sırasında iki folikül gelişimi dalgası sergilediğini ve %32'ye varan oranda üç foliküler dalga olduğunu göstermiştir.(Baerwald vd., 2003) Bu yeni paradigma ile rastgele başlangıç, östrojen duyarlılığı olan kanser hastalarında stimülasyon, geç foliküler faz stimülasyonu (FPS), luteal faz stimülasyonu (LPS) ve çift stimülasyon (DuoStim) gibi yeni over stimülasyon protokolleri (Şekil 2) geliştirilmiştir. Bu stimülasyon protokolleri, en kısa süre içinde mümkün olan en fazla sayıda oositin elde edilmesini amaçlamaktadır.

1.Rastgele uyarım

Gonadotropinler geleneksel ovaryan stimülasyonda genellikle erken foliküler faz sırasında başlatılır. Rastgele stimülasyonda, adından da anlaşılacağı gibi, over stimülasyonu adet döngüsü sırasında herhangi bir zamanda başlatılır (Şekil 2).

Genellikle kanser hastaları için doğurganlığın korunması gibi acil durumlarda kullanılır; burada over stimülasyonu, kanser tedavisini geciktirmeye gerek kalmadan adet döngüsü sırasında herhangi bir noktada rastgele başlatılabilir. Ayrıca luteolizisin, adet döngüsünün gününe bakılmaksızın, ekzojen gonadotropinlere başlamadan önce GnRH antagonisti (Fridén & Nilsson, 2005) uygulanması ile veya aynı zamanda hem GnRH antagonisti hem de gonadotropinlerin(Von Wolff vd., 2009) uygulanmasıyla indüklenebileceği öne sürülmüştür. Rastgele başlangıçlı kontrollü over stimulasyonun erken foliküler fazda başlanan geleneksel başlangıç rejimleri kadar etkili olduğu gösterilmiştir (İsrafilova vd., 2021; Kasum vd., 2014; Kim vd., 2015; Muteshi vd., 2018; Robertson vd., 2016)

2.Östrojene duyarlı kanser hastalarında over stimulasyonu

Gonadotropin ile kontrollü over stimulasyonu, östradiol seviyesinde kısa süreli suprafizyolojik bir artışa neden olarak fizyolojik seviyelerden 10-20 kat daha yüksek seviyelere ulaşmaktadır. Bu durum östrojene duyarlı kanserlerde tümör büyümesinin hızlanmasına ilişkin endişeleri artırmaktadır(Sonmezer & Oktay, 2006)

Bir aromataz inhibitörü olan letrozolün, östradiol seviyelerinin zararlı etkisini azaltmak ve over stimülasyonu sırasında güvenlik marjını artırmak için over stimülasyonu sırasında takviye edilmesi önerilmiştir. Letrozol ile yapılan over stimülasyonunun östradiol seviyelerini önemli ölçüde azalttığı gösterilmiştir. Genellikle, stimülasyonun ilk gününden ovülasyonun tetiklendiği güne kadar 5 mg letrozol doz verilir ve östradiol seviyesi hala> 50 pg/mL ise yeniden başlanır.

Steroid olmayan bir trifeniletilen anti-östrojen olan tamoksifen, hedef dokulardaki östrojen reseptöründe bağlanma bölgeleri için östrojen ile rekabet eder. Geçmişte ovülasyon indüksiyon ajanı olarak kullanılmıştır. Meme kanseri tedavisinde tamoksifen adjuvan tedavi olarak verilir ve östrojen reseptörü pozitif tümörü olan premenopozal hastalarda meme kanseri nüksünü etkili bir şekilde azalttığı ve uzun dönem sağkalımı iyileştirdiği gösterilmiştir. (Oktay vd., 2005)Tamoksifenin hem over indükleyicisi hem de anti-neoplastik bir ajan olarak doğası gereği oosit veya embriyo kriyoprezervasyonunda kullanılabileceğini göstermiştir.

Östrojen duyarlı kanser hastalarının fertilitesinin korunması amacıyla, gonadotropinlerle birlikte letrozol veya tamoksifen ile kontrollü over stimulasyonu, iyi tolere edilir ve yüksek östrojen maruziyeti riskini en aza indirirken standart protokollere kıyasla benzer sayıda oosit ve embriyo sağlar.(Cakmak & Rosen, 2015)

3.Luteal faz stimülasyonu (LPS)

Over yanıtı zayıf olan kadınlarda kısa ve uzun agonist protokolleri, antagonist protokolü, hafif stimülasyon ve dehidroepiandrosteron (DHEA) veya büyüme hormonu (GH) gibi çeşitli adjuvanların kullanımı dahil olmak üzere çeşitli overyan stimülasyon protokolleri denenmiştir, ancak bunların hiçbirinin diğerlerinden üstün olduğu kesin olarak gösterilememiştir. Bununla birlikte, yakın zamanda tanıtılan iki stimülasyon stratejisi kayda değerdir.

İlk strateji luteal faz stimülasyonudur (LFS). Menstrüel döngü sırasında herhangi bir zamanda rastgele başlatmanın başarısı, foliküler faz stimülasyonunun (FFS) ve luteal faz stimülasyonunun

(LFS) ortaya çıkmasına neden olmuştur (Şekil 2). FFS dominant folikülün seçilmesinden sonra veya ovülasyondan hemen önce kontrollü over stimulasyonun başlatılmasını ifade ederken, LFS, kontrollü over stimulasyonunun luteal faz sırasında (yani döngünün 17. ila 21. günü) başlatılmasını tanımlar. Bu stimülasyon yöntemleri, mümkün olan en kısa sürede toplanan oosit sayısını en üst düzeye çıkarmak için over rezervi azalmış veya daha önce kötü yanıt vermiş kadınlarda yaygın olarak kullanılır. Ovaryan stimülasyona geç foliküler veya luteal fazda başlanmasının diğerine karşı herhangi bir üstünlüğü olmadığı ve korpus luteum veya luteal faz progesteron seviyelerinin önceden belirlenmesinin senkronize foliküler gelişimi, toplanan olgun oosit sayısını, oositlerin kalitesini ve olgunlaşmasını ve/veya fertilizasyon oranlarını olumsuz etkilemediği görülmüştür.(Cakmak & Rosen, 2015; Cavagna vd., 2018; Checa vd., 2015; Nakasuji vd., 2019; Nazarenko vd., 2021; Pereira vd., 2017) Bununla birlikte, yayınlanan bazı çalışmalarda, luteal faz stimülasyonunun (LPS) oosit kalitesinden ödün vermediği veya gebelik sonuçlarını olumsuz etkilemediği görülmesine rağmen (Chen vd., 2015; Martínez vd., 2014) daha uzun stimülasyon ve daha yüksek dozlarda total gonadotropin gerektirdiği gösterilmiştir. (Boots vd., 2016) Bu nedenle, luteal faz stimülasyonuna başlamadan önce hastayı olası sonuçlar hakkında bilgilendirmek önemlidir.

4.Duo Stim

İkinci strateji, tek bir siklusta iki ardışık over stimülasyonunun gerçekleştirildiği DuoStim'dir. Duostim'in amacı, tek bir ovulasyon döngüsünde toplanan oosit sayısını en üst düzeye çıkarmak veya hiç oosit alınamayan veya geleneksel luteal faz stimülasyonundan sonra yeterli embriyolar üretilemeyen hastaları kurtarmaktır. Kuang ve arkadaşları 2014 yılında Şangay

Protokolünü geliştiren ilk kişilerdir (Şekil 2). Bu protokolde, ilk stimülasyon konvansiyonel bir foliküler faz stimülasyonu (FFS) iken, luteal faz stimülasyonu (LFS) ise ilk oosit toplanmasını takip eden gün iki veya daha fazla antral folikül tespit edildiğinde başlar. FFS klomifen sitrat 25 mg/gün (siklusun 3. gününden itibaren ve ovulasyonun tetiklendiği güne kadar), letrozol 2.5 mg/gün (3. günden itibaren toplam 4 gün boyunca) ve hMG 150 IU/gün (6. günden itibaren tetikleme gününe kadar gün aşırı) uygulanır. LFS ise letrozol 2.5 mg/gün ve hMG 225 IU/gün günlük olarak, her ikisi de ilk oosit alımının yapıldığı günden başlayarak ikinci ovülasyon tetiklenmesine kadar devam eder. Hipofiz down regülasyonu için medroksiprogesteron asetat da uygulanır. Her iki stimülasyon için de foliküler olgunlaşma sağlandığında ovulasyon 0.1 mL triptorelin ile tetiklenmiştir. DuoStim ilk uygulanan standart kontrollü over stimulasyonu sırasında hiç oosit alınmayan bazı kadınlarda luteal fazda daha fazla ve muhtemelen iyi kalitede embriyo üretimiyle sonuçlanabileceğinden klinik sonuçları kötü olan hastalarda psikomental yükü azaltma açısından avantaj sağlamaktadır(J. Zhang, 2015)Yakın zamanda yapılan bir sistemik derlemede, bağımsız çalışmalardan elde edilen veriler, kötü prognozlu hastalarda bu yaklaşımının tutarlılığını ve tekrarlanabilirliğini ortaya koymuştur.(Vaiarelli vd., 2020) Mevcut kanıtlar, LFS'da toplanan oosit sayısının eşleştirilmiş FFS ile toplanan oosit sayısından daha büyük olduğunu, blastülasyon ve öploidi oranları açısından da karşılaştırılabilir bir yeterlilik gösterdiğini vurgulamıştır.(Ubaldi vd., 2016) (Vaiarelli vd., 2018)

Sonuç

Özetle, günümüzde tüp bebek tedavisinde kullanılmak üzere farklı ovaryen stimülasyon tedavi protokolleri mevcuttur.

Klinisyenler, her bir protokolle ilişkili avantaj ve dezavantajları iyi anlamalı ve her hasta için bireyselleştirilmiş en uygun yöntemi seçmelidir.

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CHAPTER V

Endometrıal Cancer

Cem Yagmur OZDEMIR[1]

1.Introduction

Uterine cancer is defined as occurring in the uterus and can arise from the endometrium or from the myometrium (Anibor, 2020). In 2024, American Cancer Society estimated that 67,880 new cases would be diagnosed in the United States (Siegel, Giaquinto & Jemal, 2024). Due to the increase in life expectancy and obesity worldwide, the incidence of endometrial cancer is also increasing (Kiesel et al., 2020). US projections for the coming decades predict a 50% rise in incidence to 2030 (Sheikh et al., 2014). Most cases occur between 65 and 75 years of age. Most of the incidence and prevalence studies in the literature have been conducted on uterine cancer in general. The most common histological type of uterine cancer is endometrial adenocarcinoma. (Crosbie et al., 2022).

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2.Histopathology and molecular classification

There are two histological subtypes of endometrial cancer that differ in incidence, response to estrogen, and prognosis. Type 1 endometrial cancer includes grade 1 and 2 tumors. These tumors usually develop on the basis of endometrial hyperplasia and estrogen-sensitive. Type 2 endometrial cancer constitutes 10-20% of EC. These tumors are generally high grade and have a poor prognosis. Grade 3 includes endometrioid tumors and additionally non-endometrioid tumors (Johnson et al., 2020). Recent years have seen an exponential improvement in our understanding of the pathogenetic basis of endometrial carcinomas. Molecular characterization by The Cancer Genome Atlas (TCGA) has led to a shift from the traditional classification of Types 1 and 2 endometrial cancer to one that reflects its more heterogeneous nature. Polymerase epsilon (POLE)-ultramutated, MSI (Microsatellite instability) hypermutated, copy-number low and copy-number high are the subgroups of this molecular classifcation (Levine et al., 2013). Molecular markers can be used to predict recurrence risk and survival. It has been found that adding molecular classification to pathological diagnosis may be very important in improving the clinical approach of cases with endometrial cancer. The group with POLE mutations and the corresponding “ultra-mutated” phenotype gives very favorable results even in high-grade tumors. In 2015, Talhouk et al. developed the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), which demonstrates an easy classification system for endometrial cancer. POLE-ultramutated (POLEmut), mismatch repair deficient (MMRd), p53-abnormal (p53abn) and No Specific Molecular Profile Subgroup (NSMP) are the subgroups of this molecular classification (Talhouk et al., 2015).

Piulats et al. propose the incorporation of TCGA molecular classification as an option for assessing prognosis in endometrial cancer patients. They found that disease specific survival was 100% in the POLEmut group, 82% in the microsatellite instability group, 42.9% in the serous like group and 77.8% in the copy-number low group (Piulats et al., 2017). LeonCastillo et al. reported that 5-year recurrence rates was 36.7% for cases with p53 abnormal group, 0% for POLEmut group, 13.4% for MMRd group and 42.9% for NSMP group (Leon-Castillo et al., 2022). The molecular distribution of endometrial cancer in a study by Jamieson et al, including 172 patients, was as follows: 21 POLEmut (12.2%), 47 MMRd (27.3%), 74 NSMP (43.1%) and 30 p53mut (17.4%). They found that molecular classification in endometrial cancer was associated with lymph node metastasis and that molecular classification could be obtained in preoperative biopsies (Jamieson et al., 2022). The new World Health Organization (WHO) classification, published in 2020, acknowledges these molecular developments in the subclassification of endometrial cancer (Board, 2020). WHO 2020 endometrial cancer classification is summerized in table 1.

Table 1: WHO 2020 classification of endometrial epithelial tumours

Endometrioid carcinoma POLE-ultramutated endometrioid carcinoma Mismatch repair-deficient endometrioid carcinoma P53-mutant endometrioid carcinoma No specific molecular profile (NSMP) endometrioid carcinoma
Serous carcinoma NOS
Clear cell adenocarcinoma NOS
Mixed cell adenocarcinoma
Carcinoma, undifferentiated, NOS
Squamous cell carcinoma NOS
Mesonephric adenocarcinoma
Mesonephric-like adenocarcinoma
Mucinous carcinoma, intestinal type
Carcinosarcoma NOS

Reference: Board, E. (2020). Female genital tumours. WHO Classification of Tumours (International Agency for Research on Cancer).

The most significant change to subclassification of endometrioid endometrial cancer is the recognition of the 4 molecular subtypes; it is recommended that endometrioid endometrial cancer, in particular high-grade endometrioid endometrial cancer, should be classified into molecular subtypes, as described above, where resources permit. While grading of endometrial cancer remains unchanged; some additional details that alter prognostication have been recommended. International Federation of Gynecology and Obstetrics (FIGO) grading, as previously, is based on the extent of solid, non-squamous architecture: < 5%, 5% - 50% and >50% defining grades 1, 2 and 3 respectively. Binary grading is recommended, with FIGO grades 1 and 2 constituting low-grade endometrioid endometrial cancer and grade 3 tumours constituting high grade (Board, 2020).

Serous cancers are the second most common histopathological type of endometrial cancer and account for

approximately 10% of cases. Serous carcinoma is not graded as it is high-grade by definition. The vast majority of serous endometrial cancer demonstrate P53 mutations. Except for tumors confined to the endometrium, serous carcinoma carries a high risk of death and recurrence regardless of stage and the presence or absence of lymphoscular space invasion (LVSI) (de Boer et al., 2019). LVSI is the presence of tumor cells in the ducts surrounded by endothelium outside the main tumor in the uterus (Sadozye et al., 2016). Recently, the criterion of "≥ 4 LVSI involved vessels in at least one hematoxylin & eosin (H&E) section" has been proposed to define clinically significant LVSI (Peters, 2022).

Clear cell carcinoma is a subtype with imprecise diagnostic criteria and likely variation in diagnostic thresholds. Clear cell carcinomas are characterized by tubulocystic, papillary or solid patterns. (Murali et al., 2019). Clear cell carcinomas are also considered high grade and have a worse prognosis (Goto et al., 2012).

The designation of "mixed carcinoma of the uterine corpus" applies when two discrete histological types are identified, at least one of which is either serous or clear cell. Four subtypes were added to the new classification: mesonephric adenocarcinoma, mesonephric-like adenocarcinoma, squamous cell carcinoma and mucinous carcinoma, and gastrointestinal type (Board, 2020). Mesonephric and mesonephric-like adenocarcinom share many morphological, immunohistochemical and molecular similarities, however mesonephric carcinoma shows definite evidence of mesonephric remnants, which is not identifiable in mesonephric-like carcinoma (Howitt & Nucci, 2018). Like the mesonephric

carcinomas, squamous cell carcinoma is exceedingly rare in the uterine corpus. Risk factors include chronic inflammatory conditions, previous irradiation, and human papillomavirus (HPV) infections. In mucinous carcinomas correct recognition is important, firstly to exclude cervical or gastrointestinal tract origin, and secondly, as these are reported to be related with aggressive clinical behaviour and should therefore not be misdiagnosed as lowgrade endometrioid endometrial cancer (Board, 2020).

Uterine carcinosarcomas are malignant, mixed epithelial-mesenchymal tumors that constitute approximately 3-4% of all uterine malignancies (Kernochan & Garcia, 2009). Although the carcinoma component is consistent with known types of endometrial cancer, such as endometrioid or serous carcinoma, the sarcoma component may show homologous or heterologous differentiation (Ferguson et al., 2007). The reclassification of carcinosarcoma as endometrial cancer as opposed to mixed epithelial and mesenchymal malignancy has been one of the most significant changes (Board, 2020).

3.Risk factors

Many risk factors have been associated that cause the development of endometrial cancer. In general, risk factors are directly and/or indirectly related to an excessively estrogenic environment (Dörk et al., 2020).

Factors that increase exposure to unopposed estrogen increase the risk of endometrial cancer. Unopposed estrogen may be exogenous or endogenous. It has been suggested that there are two pathogenetically different types of endometrial cancer (Oliva et al., 2022). The most common type is found in young perimenopausal

women with a history of unopposed estrogen. In these cases, the tumor starts as hyperplasic endometrium and progresses to cancer. Estrogen-dependent tumors have a better prognosis than tumors without hyperestrogenism. The other type of endometrial cancer occurs in women who lack an endometrium-stimulating source of estrogen. These spontaneously occurring cancers are not pathologically associated with endometrial hyperplasia, but can develop from atrophic endometrium (Aguilar et al., 2022).

Obesity is a important risk factor associated with endometrial cancer. In the extraglandular area, especially in adipose tissue, androgens can be converted to estrone, which is assumed to create a very suitable environment for endometrial cancer formation. Trezions et al. showed that the complicated relationship between insulin resistance, obesity and endometrial cancer, it is obvious that maintaining healthy body weight and treating insulin resistance can help to reduce the risk of endometrial cancer (Tzenios et al., 2023). Kokts-Porietis et al. found that higher body mass index (≥30 kg/m2) was related with increased all-cause mortality and recurrence in endometrial cancer (Kokts-Porietis et al., 2021). Fat distribution in the body also affects the risk of endometrial cancer. The amount of fat accumulated in the upper body half is a significant risk factor (Cheng et al., 2022). But Donkers et al. showed that high visceral fat percentage in high-grade cancer was an independent predictor of poor survival only in non-endometrioid type endometrial cancer (Donkers et al., 2021).

The average age of menopause is difficult to determine. The average age of menopause has been determined to be 50-52 years in prospective studies (Daan & Fauser, 2015). Late menopause and

early menarche result in the endometrial cavity being stimulated by estrogen for a longer period of time. (Ring et al., 2022). Additionally, some studies have found that the risk of endometrial cancer increases 1.6 times in those who menarche before the age of 12 (Abdol Manap et al. 2022).

The fact that there is more anovulation in nulliparas is the possible reason for the increased risk. It can be expected that the frequency of endometrial cancer will decrease as the number of pregnancies increases, as a result progesterone during pregnancy, balancing estrogen and keeping the endometrium away from proliferative effects. The risk is 5 times higher than in women who have given birth five or more times. (Lambe et al.,1999).

Diabetes has been related with a statistically significantly increased risk of endometrial cancer in most, but not all studies. Zhao et al showed that the risk of endometrial cancer in endometrial hyperplasia, patients is high, especially for those patients with age >50 y, BMI ≥ 25 kg/m2 , diabetes, hypertension and severe hyperplasia, special attentions should be paid for occurrence of endometrial cancer and early diagnosis and early treatment are needed for those patients (Zhao et al., 2021). Friberg et al. supported the association between diabetes and increased endometrial cancer in their meta-analysis (Friberg et al., 2007). Saed et al showed that diabetes was related with increased risk of endometrial cancer (RR = 1.72, 95% CI 1.48–2.01) (Saed et al., 2019). In a recent review, McVicker et al. found that diabetes is related with a worse cancer specific and overall survival in endometrial cancer patients (McVicker et al., 2022).

Risk of endometrial cancer increases in women with increased endogenous estrogen levels. The increased risk is associated with chronic anovulation and also with obesity. The relative risk in women with chronic anovulation was found to be 3.1 (Coulam et al., 1983). The risk of developing endometrial cancer is 2.7 times higher in women with polycystic ovary syndrome (PCOS) (Dumesic & Lobo, 2013). Haoula et al. in their meta-analysis, they showed an increased risk of endometrial cancer in women with an odds ratio of 2.89 and a 95% confidence interval of 1.52-5.48 (Haoula, Salman, & Atiomo 2012).

It is known that long-term untreated exogenous estrogen use can cause endometrial cancer, as a result of research that gained intensity especially in the mid-1970s. However, cases of EC seen in women receiving estrogen replacement therapy were first published in the 1960s. (Gusberg & Hall, 1961). In cohort and case-control studies conducted to date, the incidence of endometrial cancer in women receiving progesterone-unopposed estrogen therapy increases by 1.4 to 10 times compared to women receiving no replacement therapy (Persson et al., 1989).

Smoking reduces the risk of endometrial cancer. The possible reason for this reduced risk is that nicotine accelerates estrogen metabolism in the liver and increases its destruction. The effect of smoking was monitored regardless of menstrual status or exogenous estrogen intake (Felix et al., 2014).

Use of combined oral contraceptives (COC) is another condition that has been shown to reduce the risk of endometrial cancer. It has been conclusively reported that COC pills reduce the risk of endometrial cancer (Kamani, Akgor, & Gültekin,2022).

Endometrial cancer risk is reduced 50–70% by 4–12 years of COC use (Dumesic & Lobo, 2013).

Tamoxifen is a potent drug to treat and prevent hormone dependent breast cancer. Tamoxifen is one of the most preferred anticancer drugs worldwide due to its low toxicity. However, an important gynecological side effect of Tamoxifen is that it increases the risk of endometrial cancer (Emons, Mustea & Tempfer 2020). Tamoxifen, which has been used in the treatment of breast cancer since the 1980s, was revealed to be associated with endometrial cancer in 1985 (Killackey, Hakes & Pierce, 1985). Specifically, tamoxifen therapy of postmenopausal patients with breast cancer is related with an high risk of endometrial hyperplasia. In a study of 238 patients treated with tamoxifen, the risk of simple and complex endometrial hyperplasia was 12% and 3%, respectively (Cohen et al., 1999).

Endometrial hyperplasia is the precursor lesion for endometrioid adenocarcinoma of the endometrium (Nees et al., 2022). Pathologists have attempted to classify the spectrum of proliferation in glands between the normal proliferative phase and carcinoma. For this purpose, structural features such as endometrial gland shapes and gland density within the stroma and cytological features such as cell stratification, nuclear growth, pleomorphism in the nucleus, nucleolus prominence and mitotic activity were used (Zaino, 2000). Many classifications have been proposed for proliferative lesions of the endometrium. Among these, the classification proposed by Kurman et al. and accepted by the WHO in 1994 is the most widely known and used today (table 2). Hyperplasias are divided into 4 subgroups: simple without atypia,

complex without atypia, simple atypia and complex atypia, with different risks of progression to carcinoma (Kurman, Kaminski, & Norris, 1985).

Information obtained through clonality studies in endometrial hyperplasia has led to the view that some of the lesions are precancerous. Mutter et al., in their revolutionary study for hyperplasia classification, simultaneously evaluated histopathological examination, clonality examination and quantitative methods in endometrial cancer precursor lesions (Mutter et al., 2000). Five easily applicable criteria have been published for the diagnosis of endometrial cancer-precursor lesions, which coincide with clonality findings and morphometric measurements. Lesions that meet these criteria are defined as endometrial intraepithelial neoplasia (EIN) (Mutter, 2002). The WHO published a new and simplified classification of endometrial hyperplasia in 2014, which consists of only two categories of hyperplasia: with and without atypia (Zaino et al., 2014). New WHO 2014 classification of endometrial hyperplasias: 1. non-atypical endometrial hyperplasia (benign hyperplasia), 2. atypical endometrial hyperplasia or (EIN) / well differentiated carcinoma.

Table 2: Classification of endometrial hyperplasia

Hyperplasia Type	**Cancer progression rates**
Simple hyperplasia without atypia	1%
Complex hyperplasia without atypia	3%
Hyperplasia with simple atypia	8%
Hyperplasia with complex atypia	29%

Reference: Kurman, R. J., Kaminski, P. F., & Norris, H. J. (1985). The behavior of endometrial hyperplasia. A long term study of "untreated" hyperplasia in 170 patients. Cancer, 56(2), 403-412.

4.Clinical symptoms and Diagnosis

The average age at diagnosis of endometrial cancer is 63 years, and more than 90% occur in women over 50 years of age. Endometrial cancer is rarely seen at a young age, with only 4% of cases occurring under the age of 40 (Lee et al., 2007). Endometrial cancer typically presents as abnormal uterine bleeding in postmenopausal women and women in the later stages of the premenopausal period (Ozdemir et al., 2023). Amount of bleeding does not correlate with cancer risk (Clarke et al., 2018). While 3-20% of women with postmenopausal bleeding have endometrial cancer; endometrial hyperplasia is detected in 5-15% of cases (Ronghe & Gaudoin, 2010).

Endometrial cancer can rarely be diagnosed by clinical evaluation. On physical examination, it is seen that the majority of patients are obese, hypertensive and postmenopausal (Barbone, Austin & Partridge, 1993). Among asymptomatic women at average risk of endometrial cancer, population-based screening has no role in early detection of endometrial cancer (Smith, Cokkinides & Brawley, 2009). Many studies have been conducted on routine control sonographies of postmenopausal asymptomatic women. However, although using a 3.0 to 5.9 mm cutoff results in a lower specificity, the offsetting improvement in sensitivity may justify using this cutoff for further endometrial evaluation in patients with suspected endometrial malignancy (Vitale et al., 2023).

All patients with postmenopausal bleeding or pyometra, asymptomatic postmenopausal patients with endometrial cells detected in their smears, perimenopausal patients with increasingly heavy menstrual periods or intermenstrual bleeding, and especially

patients with abnormal uterine bleeding with a history of anovulation should be evaluated for endometrial cancer. Abdominal examination is generally negative unless there is ascites and liver and omentum metastases in advanced stages. The uterus can sometimes be detected as a soft mass rising from the pelvis to the midline due to hematometra. Although the uterus may be globally large, it is generally of normal size. A rectovaginal examination must be performed to evaluate the uterine tubes, ovaries and cul-de-sac. Endometrial cancer metastases may occur to these areas. In addition, granulosa cell tumor, thecoma and epithelial ovarian cancers may occur together coincidentally. Attention should be paid to areas where metastases are common (Crosbie et al., 2022).

Dilation and curettage (D&C) has been the most commonly used method for endometrial sampling. Recaimer first introduced D&C in 1843. It is still widely used today. End-stage disease prediction is also better with D&C. However, the false negative rate of D&C for the diagnosis of endometrial cancer can be as high as 2-6% (Hill, 2020).

Although they are not the most preferred methods in the diagnosis of endometrial cancer, brushing, washing or exfoliative cervical cytology are used for uterine cytology. A 50% rate of false negative smears has been detected in patients with endometrial cancer. Only about 30-50% of women with endometrial cancer have malignant cells in the Papanicolaou smear. However, compared to patients with normal cervical cytology, myometrial invasion is deeper, tumor grade is higher, peritoneal cytology is positive and the disease is at a more advanced stage in patients with suspicious or malignant cells (Koss et al., 1981).

The presence of normal endometrial cells, as well as the presence of abnormal cells in the cervical smear taken in the second half of the menstrual cycle or in the postmenopausal period, should alarm the clinician about the possibility of endometrial disease. If morphologically abnormal endometrial cells are present, approximately 25% of women have endometrial cancer. Ashfaq et al. in their study on 146 postmenopausal women with benign endometrial cells in their cervical smears, they found benign endometrial pathologies such as polyps, leiomyomas, and simple hyperplasia without atypia in 28% of the cases, while atypical hyperplasia, adenocarcinoma, leiomyosarcoma, and malignant mixed müllerian tumors were detected in 12% of the cases (Ashfaq et al., 2001).

Histological sampling is very easy to perform as it can be done in office conditions and is economical. Although it can be done without the need for anesthesia, paracervical block is sufficient when necessary. Although it is popular today to perform it with negative pressure applied to the aspiration curette, gentle curettage with a Kevorkien curette, which is not an aspirator type, is also successful. Endometrial biopsy is insufficient to recognize endometrial polyps and endometrial hyperplasia may be missed. Therefore, when there is insufficient tissue for diagnosis or when accurate staging cannot be achieved with this method, fractionated curettage should be performed (Goldstein, 2010).

Devices such as Vabra aspirators are usually aspiration devices with a 3-4 mm diameter plastic or rigid metal cannula that can be connected to a vacuum source. A negative pressure of approximately 300-600 mmHg is used when taking endometrial

biopsy with the Vabra aspirator. Its effectiveness varies between 95-98%. A 6-7% deficiency is observed in samples taken with this method. Pipelle is a softer and more flexible endometrial suction curette. The Pipelle device is a device preferred by many clinicians because it is well tolerated by patients and provides sufficient samples. Clark et al. examined a total of 11 studies containing over 1000 endometrial biopsy cases and found the positive predictive value for endometrial biopsy to be 81%. They detected endometrial cancer in less than 1% of negative biopsy results, so they decided that endometrial biopsy was an appropriate method (Clark et al., 2002).

The fact that the hysteroscopy procedure is easy to perform, does not cause any adverse effects on the patient's comfort, and can be applied in office conditions has enabled the more frequent use of this method among physicians. The advantage of the method is that the uterine cavity can be directly monitored and a biopsy can be taken from the suspicious area. As a result of the studies, more positive results were obtained in the diagnosis of endometrial cancer compared to the diagnosis of endometrial hyperplasia. Hysteroscopy and D&C should be performed in the presence of recurrent postmenopausal bleeding despite negative histology in blind endometrial sampling, in cases where sufficient material cannot be obtained to explain abnormal bleeding, and in the presence of cervical stenosis. Cervical stenosis may cause problems in 3-5% of cases (Saccardi et al., 2020).

The hysteroscopic appearance of endometrial cancer is distinct and difficult to confuse with other lesions. In the initial stage of adenocarcinoma, the appearance is irregular, polylobulated,

necrotic and prone to bleeding. The vascularization is irregular and unformed. In some cases, a demarcation line is evident between normal endometrium and neoplasia. While focal lesions in the corn can sometimes be missed when blind sampling techniques are used, they can be easily diagnosed with hysteroscopy. It was once suggested that malignant tumor cells in endometrial cancer patients could spread to the peritoneal cavity through reflux from the fallopian tubes with distention medium through hysteroscopy. Zerbe et al retrospectively examined data from 222 patients with endometrial cancer to investigate the effect of preoperative hysteroscopy on the frequency of positive cytology during surgical treatment. As a result, it was stated that hysteroscopy significantly increased the incidence of positive peritoneal cytology, especially in patients with high-risk cell types (Zerbe et al., 2000). Recent studies have proven that hysteroscopy is a safe diagnostic method for patients with endometrial cancer, with no impact on oncological outcomes compared to Pipelle sampling (Quintana-Bertó et al., 2022).

Ultrasonography is the basic examination method of gynecological organs and is a simple, painless and non-invasive technique with no radiation effect. Ultrasonography is the acquisition of images by reflecting high-frequency sound waves from anatomical structures. It is applied transvaginally, transabdominally, transperineally and transrectally. All layers of the uterus, including the myometrium, its outer contour, the ovary, and other pelvic and abdominal organs can be examined. Evaluation of the source and characteristics of pelvic masses, endometrial and myometrial lesions, pelvic inflammatory disease, folliculometry, and determination of intrauterine device localization are the basic

indications of ultrasonography. Transvaginal ultrasonography eliminates the factors that cause limitations in transabdominal examination of the pelvis, such as obesity, gas, and position anomalies of the uterus, and provides detailed evaluation of the genital organs (Cerovac et al., 2022). The normal endometrial cavity is observed as a thin echogenic line as a result of the interface mirror reflection between mutual endometrial surfaces. The sonographic appearance of the endometrium changes in accordance with its histology during the menstrual cycle (Sibal, 2017).

Doppler sonography is also a method used in the diagnosis of gynecological tumors. Color Doppler combines the grayscale image with the image generated by blood flow. By color coding the frequency shifts, flow direction and turbulence can be easily identified. Blood flow can be detected in the area where progressively growing tumoral tissue exists. An attempt is made to differentiate between malignant and benign by examining the pulsatility index (PI) and resistance index (RI) values calculated from the waveform and whether there is a diastolic notch. Minimal resistance that develops in diastole in vessels with normal wall layers is reflected as notching on doppler ultrasonographic examination.

Magnetic resonance imaging (MRI) and computed tomography (CT) are useful methods in determining local and distant spread in endometrial carcinoma. They are useful in relapses and especially in the evaluation of regional lymph nodes. It is more difficult to detect tumors, especially small sizes, with MRI because they have the same density as normal endometrium. Large tumors are easier to detect with MRI, and extension to the cervix, myometrium, and parametrium can be detected much more

accurately. In particular, it is possible to distinguish between stage 1 and stage 2 with higher accuracy with MRI (Laifer-Narin et al., 2018).

6.Staging

Endometrial carcinoma is surgically staged and the staging procedure includes total hysterectomy, bilateral salpingo-oophorectomy, and lymphadenectomy. A comprehensive examination of the abdominal area should be performed to exclude extrauterine diseases. Abnormal surfaces, including diaphragmatic surfaces, peritoneal and serosal surfaces, should be biopsied. Omental biopsies are generally recommended for those with high-risk histopathologies (eg, serous, clear cell, or carcinosarcoma). Peritoneal cytology is usually sampled during surgery; but no longer affects the staging of the disease (Takenaka et al., 2021). LVSI, cytology and molecular markers were not in the FIGO 2009 EC staging system (Pecorelli, 2009). The old FIGO 2009 staging is shown in table 3.

Table 3: FIGO 2009 Staging System for Endometrial Cancer

Stage I	Tumour limited to the uterus
IA	No or <50% myometrial invasion
IB	≥50% myometrial invasion
Stage II	Cervical stromal invasion, but not beyond the uterus
Stage III	Local and/or regional tumour spread
IIIA	Tumour invades serosa and/or adnexa
IIIB	Vaginal and/or parametrial involvement
IIIC	Metastases to pelvic and/or para-aortic lymph nodes
IIIC1	Pelvic node involvement
IIIC2	Para-aortic lymph node involvement
Stage IV	Tumour invades bladder and/or bowel, and/or distant metastases
IVA	Tumour invasion of bladder and/or bowel mucosa
IVB	Distant metastases including abdominal metastases / inguinal metastases

Reference: Pecorelli, S. (2009). Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium.

LVSI is a marker of nodal disease in endometrial cancers and is considered an independent risk factor for recurrence and death in all stages of the disease. In stage 1 endometrial carcinoma cases, LVSI has been correlated with high mortality rates. Briët et al. reported that patients with LVSI are more likely to have pelvic lymph node metastases (PLNM) compared to those without LVSI, and relapses occur more frequently in patients with LVSI (Briët et al., 2005). Ozdemir et al. showed that for patients negative for LVSI, the progression-free survival rate was 93%, while for LVSI-positive patients, it was 77.3% (Ozdemir et al., 2024). Raffone et al. reported that LVSI has a prognostic value independent of TCGA signature, as well as age and adjuvant treatment, increasing the risk of death of any cause, death due to endometrial cancer, and recurrent or progressive disease by 1.5–2 times (Raffone et al., 2022). In 2023, FIGO published a new staging system for endometrial cancer, which now includes LVSI as part of the new staging system (Berek et al., 2023). The criteria for LVSI follow the rules of WHO (Cree et al., 2020). Accordingly, LVSI should fall into one of the following three categories: “LVSI negative” (0 vessels); “LVSI focal” (<5 vessels); or “LVSI substantial/extensive” (≥5 vessels). The new FIGO 2023 staging is shown in table 4.

FIGO suggest that if available and feasible, molecular classification testing (POLEmut, MMRd, NSMP, p53abn) is encouraged in all patients with endometrial cancer for prognostic risk-group stratification and as factors that might influence adjuvant and systemic treatment decisions. In case the molecular classification reveals POLEmut or p53abn status, the FIGO stage is modified in the early stage of the disease. This is depicted in the FIGO stage by the addition of “m” for molecular classification, and

a subscript is added to denote POLEmut or p53abn status, as shown below (Berek et al., 2023).

7.Clinical management

Standard surgery for endometrial cancer is total hysterectomy with bilateral salpingo-oophorectomy without vaginal cuff. Ovarian preservation can be considered in patients younger than 45 years old with grade 1 endometrioid endometrial cancer with myometrial invasion. In cases of ovarian preservation, salpingectomy is recommended. Ovarian preservation is not recommended for patients with a family history of ovarian cancer risk. Lymphadenectomy is an important element in the surgical staging of endometrial cancer. However, the role of lymphadenectomy in early endometrial cancer is unclear (Colombo et al., 2016). In early-stage endometrial cancer, systematic pelvic and para-aortic lymphadenectomy does not affect oncologic outcomes, including overall survival and disease-free survival, but increases perioperative morbidity, operative time, and costs (Burke et al., 2014).

Table 4: FIGO 2023 Staging System for Endometrial Cancer

Stage I	Confined to the uterine corpus and ovary
IA	Disease limited to the endometrium OR non-aggressive histological type with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
IA1	Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
IA2	Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
IA3	Low-grade endometrioid carcinomas limited to the uterus and ovary
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI
IC	Aggressive histological typese limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI of non-aggressive histological types
IIC	Aggressive histological types with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)
IIIA2	Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
IIIB1	Metastasis or direct spread to the vagina and/or the parametria
IIIB2	Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both
IIIC1	Metastasis to the pelvic lymph nodes
IIIC1i	Micrometastasis
IIIC1ii	Macrometastasis
IIIC2	Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes
IIIC2i	Micrometastasis
IIIC2ii	Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Reference: Berek, J. S., Matias-Guiu, X., Creutzberg, C., Fotopoulou, C., Gaffney, D., Kehoe, S., ... & Mutch, D. (2023). FIGO staging of endometrial cancer: 2023. International Journal of Gynecology & Obstetrics, 162(2), 383-394.

Over the past few years, less-invasive strategies for lymph node evaluation have been investigated. Sentinel lymph node (SLN)

sampling, first described in 1996, was established to be as accurate as systematic lymphadenectomy in evaluating the nodal status of early endometrial cancer and is now the standard of care in most gynecologic oncology units (Casarin et al., 2019). SLN was considered experimental at the ESMO/ESGO/ESTRO consensus conference on endometrial cancer in 2016 (Colombo et al., 2016). However, in 2021, the ESGO/ESTRO/ESP guidelines recommended SLN for surgical staging in patients with low-risk or intermediate-risk endometrial cancer, while systematic lymphadenectomy was not recommended in this group. In patients with high-intermediate-risk or high-risk disease, SLN is considered an acceptable alternative to systematic lymphadenectomy (Concin et al., 2021).

Surgical resection remains the cornerstone of cure for endometrial cancer, with minimally invasive surgery offering multiple advantages. Laparoscopy is alternative to laparotomy. Cho et al showed that the 5-year PFS rates in the laparoscopy and laparotomy groups were 95.5% and 96.5% (Cho et al., 2007). Minimally invasive techniques have recently been proven as safe alternatives for surgical staging, with less morbidity and quick recovery. However, after the LACC (Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy) trial, there was a move away from minimally invasive, especially in early stage cervical cancer (Ramirez et al., 2018). Also after the LACC study, minimally invasive interventions began to be discussed in terms of complications. A meta-analysis showed that the incidence of urological complications in radical cervical cancer surgery was higher before the LACC trial (Bruno et al., 2023). Zouridis et al showed that laparoscopic and open surgery seem to have comparable outcomes for stage II endometrial cancer

(Zouridis et al., 2023). Haddad et al showed that laparoscopy was better than laparotomy to manage of these patients because the duration of hospitalization, blood loss and intraoperative and postoperative complications in laparoscopy procedure (Haddad et al., 2021). Additionally, Galaal et al showed in their meta-analysis that there was no significant difference in the risk of recurrence between the two groups (Galaal et al., 2018).

Robotic Surgery, an alternative surgical option, has emerged and its use in endometrial cancer is increasing. Compared to laparotomy and laparoscopy, robotic surgery resulted in shorter hospital stays and fewer complications such as blood loss. Although robotic surgery is costly and generally has longer operating times, a randomized trial found that operating times were shorter (Mäenpää et al., 2016).

Advances are also presented in fertility-sparing options for younger patients diagnosed with endometrial cancer (Stewart et al., 2020). For a fertility-sparing approach in endometrial cancer, women should be counseled that their chances of having a live birth decrease as they get older. Patients should be informed about the higher risk of persistence/recurrence as compared with other patients. Fertility-sparing treatment is considered for endometrioid patients with endometrial cancer with grade 1, stage IA without myometrial invasion and without risk factors. Magnetic Resonance Imaging (MRI) or computed tomography (CT) scan is recommended for detecting pelvic or paraaortic lymph nodes and distant metastases. Adnexal involvement should be ruled out by pelvic MRI or transvaginal ultrasound. Definitive surgery is recommended in cases of non-responders, inability to conceive, recurrence or disease

progression. Completion surgery is recommended after completing childbearing (Rodolakis et al., 2023).

Among the fertility-sparing management options, hormonal methods are frequently used, especially oral progestins, and the most common regimens are medroxyprogesterone acetate and megestrol acetate. A levonorgestrel-releasing intrauterine device can also be used (Carneiro et al., 2016). Exposure to unopposed estrogen and persistently low progesterone levels leads to molecular mechanisms responsible for the subsequent regression of hyperplasia. Therefore, progesterone has been investigated as a primary treatment for endometrial intraepithelial neoplasia or complex atypical hyperplasia and as an alternative to surgery in grade 1 endometrioid endometrial cancer (Pal et al., 2018). The levonorgestrel-releasing intrauterine device provides sustained localized levonorgestrel exposure at an initial release rate of 20 mcg/day (Chaudhari et al., 2023).

Adjuvant treatment of endometrial cancer after surgical staging includes radiotherapy, chemotherapy and immunotherapy (Kalampokas et al., 2022). Patients diagnosed with low-risk stage I endometrial cancer are not candidates for radiotherapy. Brachytherapy is recommended for intermediate-risk, high-risk, and high-intermediate-risk endometrial cancer. The presence of lymphovascular space invasion is of great importance, and external beam radiation therapy (EBRT) is also recommended (Boothe et al., 2019). Adjuvant chemotherapy is an important part of high-risk endometrial cancer treatment strategies. Carboplatin and paclitaxel are commonly used because of similar results in overall survival and progression-free survival, and they also appear to be less toxic.

While chemotherapy is generally used in combination with radiotherapy for Stage III B and III C endometrial cancer, adjuvant chemotherapy is recommended after cytoreductive surgery for resectable Stage IV disease (Lee et al., 2017). With the development of molecular classification, targeted treatments in endometrial cancer have been made possible. multi-cohort phase II study demonstrated the efficacy of pembrolizumab monotherapy, an anti-PD-1 agent, in MSI-H/dMMR advanced endometrial cancer, indicating anti-tumor activity and presenting a safe toxicity profile with a median PFS of 13.1 months (O'Malley et al., 2022). Pembrolizumab, usually administered as a single agent or in combination with other compounds, is a safe and well-tolerated drug for solid tumors (Gandhi et al., 2018). Molecular markers of tumor in endometrial cancer are a prerequisite to guide therapeutic selection of pembrolizumab. Both MMRd and MSI-H have been proposed as predictive biomarkers of response to immune checkpoint inhibition (Murali, Soslow & Weigelt, 2014). Targeting PD-1 with pembrolizumab in pretreated patients with advanced or recurrent endometrial cancer represents a promising therapeutic approach and has thus received two FDA approvals as a single agent and in combination with lenvatinib (Walker, Spirtos & Miller, 2023). When managing previously treated recurrent endometrial cancer, immunotherapy with a PD-1 inhibitor in combination with an antiangiogenic agent has been shown to be highly beneficial for patient survival. Cabozantinib-nivolumab combination therapy significantly improved progression-free survival (5.3 vs 1.9 months) according to a translational phase II study (Lheureux et al., 2022).

8.Conclusion

The incidence of endometrial cancer is increasing with increasing obesity in the world. Although there is no effective screening method for endometrial cancer, it can be diagnosed at an early stage as the majority of patients are symptomatic. With the 2023 FIGO staging, LVSI and molecular markers have now become part of the system. Hysteroscopy, which was not previously preferred due to suspicion of tubal spread, has become a follow-up and treatment option for endometrial cancer. Lymphadenectomy can still be performed but sentinel lymph node biopsy emerges as an alternative even in high-risk endometrial cancer. Great progress has been made in endometrial cancer with molecular classification, and classical histopathological classification has almost been abandoned. Today, endometrial cancer has become a disease that is monitored and treated not only surgically but also hormonally. Keeping fertility-preserving treatment in mind in endometrial cancer is important for many cases.

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CHAPTER VI

Ektopik Gebelikler

İhsan ŞAFAK[1]

Giriş

Fertilizasyonun gerçekleşmesinden itibaren fallop tüplerinden blastokistlerin normal şartlarda endometrial kaviteye yerleşmesi ve gelişmesi beklenmektedir. Endometrial kavite dışında yerleşen tüm implatasyonlar ise dış gebelik olarak tanımlanmaktadır. Birleşik devletlerde %1-2 oranında tüm gebelikler içinde dış gebelik oranı mevcuttur. Dış gebelik oluştuğunda bir sonraki gebeliğin normal bir gebelik olma şansı düşmektedir. Günümüz şartlarında erken tanı imkanlarının gelişmesi ile birlikte üreme potansiyelinin korunması sağlanmaktadır. Dış gebelikler yerleşme yerlerine göre tanımlanmaktadır. Yerleşme yerine göre tedavi de değişiklik olduğu için erken tanı çok kritik önem taşımaktadır (Stulberg, 2013).

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Tubal Gebelikler

Tüm dış gebelikler içinde fallop tüplerinin farklı yerlerinde ektopik gebelik gelişmesi durumu yaklaşık %95 oranında görülmektedir. Fallop tüplerinde fimbriyal, istmik, ampuller ve interstisyel olmak üzere yerleşim yerine göre tanımlanmaktadır. Fallop tüplerinde en fazla ampuller bölgede ektopik gebelik gelişmekte olup ampulla dışında ise istmik bölgede diğer yerlere göre daha sık görülmektedir. Tubal gebelik dışında kalan %5 kısmında ise over, periton, servikal ve sezeryan skar gebeliği gibi vücudun başka kısımlarında görülebilmektedir. Çok nadir olmakla birlikte çoğul gebelik olduğunda ise bir gebelik endometrial kavitede yerleşmiş olup diğer gebelik ise ektopik olabilmektedir. Bu gebeliklere ise heterotropik gebelik olarak tanımlanmaktadır. Normal yollarla oluşan gebeliklerde 30.000 gebelikte 1 görülmekte iken yardımcı üreme teknikleri kullanılarak oluşan gebeliklerde bu oran 7000 de 1 görülmektedir (Mukul,2007& Eze,2012).

Ektopik gebeliğin oluşmasında altta yatan asıl patoloji fallop tüplerindeki anormal yapı ve tüpün içinde bulunan yapıların asıl görevini yerine getirememesine bağlı olduğu düşünülmektedir. Bir önceki gebeliğinde ektopik gebelik oluşması durumunda veya tubal bir operasyon geçirilmesi durumunda ektopik gebelik oluşma ihtimali daha da yükselmektedir. Geçirilmiş pelvik enfeksiyonlar, salpenjit gibi durumlara bağlı olarak da ektopik gebelik gelişme ihtimali artmaktadır (Skjeldestad, 1998& Schippert, 2012).

İn-utero dietilstilbestrol maruziyetine ikincil olarak oluşan konjenital fallop tüpü anomalilerinde yüksek oranda ektopik gebelik ile ilişki bulunmuştur. Yine sigara kullanımının tam mekanizması

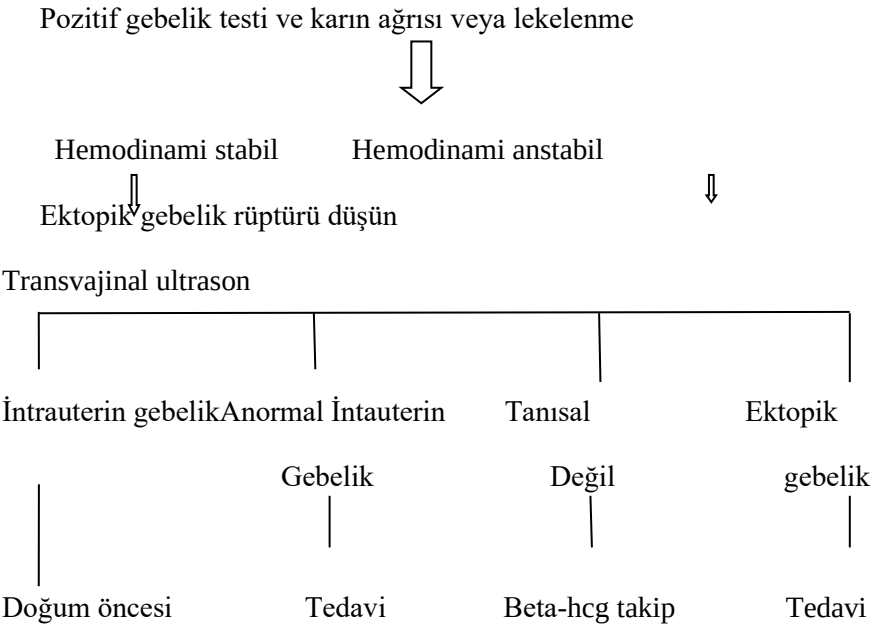
belli olmamakla birlikte ektopik gebelik ile ilişkisi olduğu bilinmektedir (Waylen, 2009& Hoover, 2011).

Tubal sterilizasyon, bakırlı ve levonorgestrelli RİA, sadece progestin içeren haplar gibi korunma yöntemlerinin başarısız olması durumunda ektopik gebelik insidansı göreceli olarak arttığı görülmüştür. Ektopik gebelik gelişmesi durumunda yerleşim yerinden bağımsız olarak Rh uygunsuzluğu mevcut ise anneye anti D immunoglobin uygulanmalıdır. Tubal ektopik gebelikte fallop tüpünde submukozal tabakasının olmaması nedeniyle fertilize yapı epitelyum tabakanın içinde oyuk açar ve trofoblastlar musküler tabakaya kadar invaze olur fertilize yapının büyümesi ile birlikte rüptür ihtimali artmaktadır. Ektopik gebelik sonrasında ise tubal rüptür ve tubal abortus veya abort sonrası rezolüsyon gerçekleşebilmektedir. Gebelik ürünü ilk birkaç hafta içinde tubada rüptür olursa genellikle gebelik ürünü tubanın istmusuna yerleşmiştir. İnterstisyel kısımda ise ise rüptür genellikle daha geç gelişmektedir. Tubal abortta kanama, membranların ve gebelik yapılarının fimbriyal uçtan tamamı atılması durumunda kanama durabilir ancak tubada gebelik ürününün bir miktar bile kalması durumunda kanamanın devam ettiği izlenmiştir. Kanama devam ettikçe cul-de-sak da kan birikir ancak fimbriyal uçta pıhtı oluşması durumunda kan atılamadığı için hematosalpenks oluşabilmektedir. (Brennan, 2000&Furlong, 2011).

Erken başvuru ve gelişen teknoloji ve sağlık sistemine ulaşılabilir durumunun artması ile erken tanı koymaya olanak sağlamıştır. Bu olgularda belirtiler daha az veya hafif olarak izlenmektedir. Klasik ektopik gebelikte ise vajinal kanama ve lekelenme görülmektedir. Rüptür ile birlikte ise şiddetli ve keskin bir

karın ağrısı, kanamanın fazla olmasıyla birlikte baş dönmelerinden bayılmaya ve şok tablosuna kadar ilerleyen tehlikeli bir durum gelişebilmektedir. Batın muayenesinde hassasiyet mevcuttur. Pelvik muayenede ise servikal hassasiyetlerde artış izlenmektedir. Bir miktar lekelenme veya kanama tubal ektopik gebelik vakalarının %60-80 kadarında olduğu gösterilmiştir. Aşırı kanama abortusun bir göstergesi iken bazı durumlarda ektopik gebelik durumunda da görülebilmektedir. Anlamlı kanama durumuna rağmen ilk başta hemoglobinde hafif düşüş izlendiği görülebilmektedir. Rüptüre dış gebelikte lökositoz anlamlı derecede arttığı gösterilmiştir. **Tablo 1** de ektopik gebeliğe yaklaşım ve yönetimi gösterilmiştir(Grynberg, 2009& Gala, 2012).

***Tablo 1**: Ektopik gebeliğe yaklaşım*



Ektopik gebelik tanısı karın ağrısına neden olan bir çok başka hastalıkla karışabilmektedir. Ektopik gebeliği tanımak için algoritmalar mevcuttur. Fizik muayene bulguları ile birlikte transvajinal bakılan usg ve beta-hcg ölçümleri artış ve düşüşüne göre ektopik gebeliğe yaklaşım değişmektedir. Yükselme ve düşüşe göre küretaj, laparoskopi ve acil laparatomi gibi bir çok seçenek mevcuttur. Tabi ki bu algoritma hemodinamik olarak stabil olan hastalarda kullanılmaktadır. Rüptür şüphesi ve anstabil olan hastalarda acil operasyon planlanmalıdır. Serum beta-hcg değeri ektopik gebelik yakınmaları olan hastalarda bizim için çok ciddi öneme sahiptir. Kanama ve ağrı ve pozitif beta-hcg değeri varlığında öncelikle transvajinal usg ile gebeliğin yeri belirlenmektedir. Uterus ve adnekslerde yolk-salk kesesi veya fetüs varlığı ile tanı konulabilmektedir (Guss, 2002).

Bazı araştırmalardan elde edilen verilere göre serum beta-hcg değerinin belli bir değerin üstünde olduğunda transvajinal usg ile gebelik kesesinin görülmesini yüksek güvenirlik aralığı ile göstermişlerdir. Genellikle beta- hcg değerinin 2000 mIU üstünde olduğunda transvajinal olarak görülmesi gerektiğini bildirmişlerdir. Bu beta-hcg değerine ise ayırt edici zon olarak tanımlanmıştır. Ayırt edici zon üstünde bir değer varlığı ve intrauterin gebelik mevcut olmadığında ektopik gebelik tanısı konulmaktadır. Ayırt edici zon aralığının altında bir değer olduğunda transvajinal usg ile kese görülmesi beklenmediğinden seri beta-hcg bakılması ve artış durumuna göre tanı konulmaktadır. Bu konuda bir çok çalışma mevcut olup bazı çalışmalarda beta-hcg değerinin 48 saatte iki kat artışının normal bir gebelik için istenen bir değer olup en düşük sağlıklı değerin ise %66' ın üstünde bir artış olması gerektiğini bildirmişlerdir. Beklenen sağlıklı gebelikte beta-hcg artışları

olmadığında veya düşüş olduğunda intrauterin canlı olmayan gebelik veya ektopik gebelik düşünülmektedir. Bu iki durumu ayırmak için seri beta-hcg ölçümü yapılmalıdır. Ayrıcı tanıda küretaj yapılması da faydalı olduğu bildirilmiştir (Seeber, 2006& Gala, 2012).

Serum progesteron değerinin birkaç kez ölçümü ile de dış gebelik açısından faydalıdır. Progesteron değerinin 25ng/ml üzerinde olması durumunda %92 nin üzerinde dış gebelik olmadığını dışlamaktadır. 5ng/ml değerinin altında olması durumunda ise normal gebeliklerin sadece %0,3 kadarında görüldüğü için 5ng/ml altında olması çok büyük bir ihtimalle sağlıklı olmayan bir gebelik durumu olduğu konusunda bilgi vermektedir. Bu değerin altında gebelik durumunda ya sağlıksız bir gebelik ya da dış gebelik açısından değerlendirilmelidir. Bu iki değer aralığında kullanımı ise klinik açıdan kullanımı çok sağlıklı değildir (Stovall, 1992& Pisarska, 1998).

Dış gebelik şüphesi olan hastaya transvajinal usg yapılır. İntrauterin veya ektopik gebeliği gösteren bulgular dikkatle incelenmelidir. İntrauterin kavitede gebelik kesesi 4 hafta ile 5 hafta arasında görülmesi beklenir. Transabdominal olarak biraz daha geç gözükmektedir. Normalde erken intrauterin bir gebelikte görülen anekoik sıvı bazen dış gebelikte de görülebilmektedir. Yapılan çalışmalarda kesin bir yolk salk kesesi görülmeden veya embriyo görülmeden intrauterin bir gebelik tanısı koyulmaması önerilmektedir (Dashhefsky, 1988& ACOG, 2023).

Dış gebeliğin adneksiyal bulgularında overden ayrı olarak adneksiyal kitle izlenmektedir.Fallop tüpleri ve overler görüldüğünde ve extrauterin bir gebelik yapısı görüldüğünde

ektopik gebelik tanısı kesin olarak konulabilmektedir. Ektopik gebelik açısından şüphe duyulduğunda hemiperitonyum açısından dikkatlice bakılmalıdır. Günümüzde genellikle usg ile tanı konulsada kesin tanı da kuldosentez ile kesinleştirilmek için uygulanabilmektedir. Transvajinal usg ile 50 cc kadar kan bile görülebilmekte olup yaygın bir batın içi kanamada transabdominal usg de yardımcı olmaktadır. Çok az miktarda ki kan bazen fizyolojiktir ayrıcı tanı açısından dikkatli olunmalıdır.Laparoskopi ciddi ektopik gebelik şüphesi olan vakalarda uygun bir tanısal işlem olup hem tanı hem de bu şekilde tedaviye olanak sağlamaktadır (Rodgerson, 200& Condous, 2005).

Ektopik Gebelikte Medikal Tedavi

Medikal tedavi rüptüre olmamış olgular için kullanılmaktadır. Ektopik gebeliği ne kadar erken tanıma imkanı olursa cerrahiye gitmeden medikal tedaviden sonuç alma imkanı daha da artmaktadır. Medikal tedavide asıl kullanılan ajan folik asit antagonisti olan metotreksattır. Trofoblast gibi hızlı çoğalan hücrelerde etkinliği yüksek olduğu bildirilmiştir. Kemik iliği, gastrointestinal mukoza gibi yapılara da olumsuz etkileri mevcuttur. Anne sütüne geçtiği için emzirme döneminde uygulanmamalıdır veya emzirme bir süre bırakılmalıdır. Dış gebelik için en sık kullanılan doz tek doz intramusküler uygulamadır. Tek doz kullanımı basit uygun lökoverin gibi ilaçların kullanımına gerek olmayan daha rahat bir uygulamadır ancak bazı çalışmalarda çoklu doz uygulanmasının başarı şansının daha yüksek olduğu bildirilmiştir.**Tablo 2** de metotreksat doz uygulamasının protokolü detaylı olarak gösterilmiştir. Metotreksat uygulamasının kontraendikasyonları ise **Tablo 3** de gösterilmiştir (Nurmohamed, 2011&Gungorduk; 2011).

***Tablo 2**: metotreksat uygulama protokolü*

	Tek doz	Çoklu doz
Doz	Tek doz gerekli ise tekrar uygulanır	Serum beta hcg değerleri %15 azalana kadar, her iki ilaç en çok 4 doz uygulanır
İlaç dozu Metotreksat Lökoverin	50mg/m2 Lökoverin uygulanmaz	1mg/kg,1-3-5-7 günlerde Lökoverin; 0,1mg/kg 2-4-6-8 günler
Serum beta hcg	1.gün(bazal) 4-7 günler bakılır	1-3-5-7.günler bakılır
Ek doz ne uygulanması	Serum beta-hcg seviyelerinde 4-7.günlerde %15 den daha az azalma izlenmese ve haftalık izlemlerde %15 kadar düşüş izlenmediğinde uygulanır	Serum beta-hcg azalması %15 den az ise beta-hcg 48 saat içinde tekrar bakılması ve bir öncekine göre değere göre bakılmalı veen fazla 4 doz uygulanır

***Tablo 3**: Metotreksat uygulamasının kontrendikasyonları*

-Metotreksak alerjisi -Emzirme -Ektopik rüptür -İntrauterin canlı gebelik	-Karaciğer, böbrek veya hematolojik fonksiyon bozukluğu -Peptik ülser -Aktif bir pulmoner hastalık varlığı -İmmün yetersizlik

Metotreksat için en uygun hasta seçimi asemptomatik erken hafta hastalar olup çok başarılı sonuçları mevcuttur. Yapılan çalışmalarda metotreksat uygulamasının over rezervini azaltmadığı

gösterilmiştir. İlaç uygulaması sonrası birkaç gün sonra başlayan ağrı hastanın yarısından fazlasında mevcut olduğu gösterilmiştir. Metotreksat tedavisi ile cerrahi tedavi karşılaştırılması için yapılan çok merkezli çalışmada fallop tüpünün korunması dışında başarısızlık açısından anlamlı bir fark bulunmadığı gösterilmiştir (Lipscomb, 1999& Hajenius, 2011).

Ektopik Gebelikte Cerrahi Tedavi

Olguların hemodinamik stabilitesi olmaması dışında dış gebeliğin asıl cerrahi yöntem olarak laparoskopi tercih edilmelidir. Laparoskopi ile laparotomi arasında az sayıda da olsa yapılan çalışmalarda her iki yöntemin karşılaştırmasında ikisi arasında başarı ve bir sonraki gebelik için herhangi bir olumsuzluk durumu iki yöntem içinde benzer olup anlamlı bir fark olmadığı gösterilmiştir.Salpingostomi gibi tüpün korunduğu cerrahi yöntemler konservatif yöntemler olarak da adlandırılır. Yapılan çalışmalarda salpenjektomi ile salpingostomi karşılaştırılması yapılmış olup ikisi arasında bir sonraki gebelik oranları açısından anlamlı bir fark olmadığı bildirilmiştir (Hajenius, 2011&Bennetot, 2012).

Salpingostomi genellikle fallop tüpünün distal üçte bir kısmında yerleşen yaklaşık 2 cm çapından küçük tubal ektopik gebeliklerde uygulanan bir yöntemdir. Yapılan bir çalışmada beta-hcg değerininin 6000mIU üzerinde musküler tabakaya invazyon oranın fazla olması nedeniyle başarı şansının düşük olduğunu bildirmiştir. Salpingostomi de en kritik nokta tüm gebelik ürünün tamamen çıkartılmasıdır (Al Sunaidi, 2007).

Salpenjektomi ise hem rüptür olmuş ektopik gebelikte hem de rüptüre olmayan gebeliklerde kullanılabilmektedir. Tubal ektopik

gebelikler esnek olduğu için endoskopik torba ile port girişinden dışarı alınabilmektedir (Thompson, 2012).

Persistan trofoplast durumu ise ektopik gebelik sebebiyle yapılan cerrahide tam olarak trofoblastların çıkartılamamasına bağlı olarak değişmeyen veya artan beta- hcg oranları ile karşımıza çıkan bir durumdur. Operasyon sonrası birinci gün bakılan beta-hcg ile operasyon öncesi beta-hcg %50 ve üzerinde düşüş izlendiğinde persistan trofoplast durumunun olması nadir olacağı bildirilmiştir (Spandorfer, 1997).

Sabit ya da azalan beta-hcg düzeylerine sahip olan erken dönemdeki hastalarda yakın takip ve beta-hcg takibi ile izlem önemlidir. Yapılan çalışmalarda bu vakalarında üçte bir oranında kendiliğinden beta-hcg düşüşü beklenmekte olup ek bir tedaviye ihtiyaç yoktur. İzlem yapmak için hemodinami stabil olmalı, batın içi kanama olmamalıdır. Yapılan bir çalışmada beta-hcg 1500mIU değerinden küçük ve gebelik ürününün 3 cm den küçük olması durumunda yaklaşık 1/3 oranında kendiliğinden gerilediği bildirilmiştir. İzlem ile diğer tedavi yöntemleri karşılaştırıldığında intrauterin canlı gebelik açısından anlamlı bir fark olmadığı bildirilmiştir (Shavel, 1995&Mavrelos, 2013).

İnterstisyel Gebelik

Bu gebelikler musküler uterin duvarın içinde bulunan, tubanın proksimal segmentinde yer alan alana implante olurlar. Bu gebelikler kornual gebelikle karıştırılabilmektedir. Aynı tarafta ektopik gebelik geçirilme öyküsü bir risk faktörüdür. Tanı konulmamış vakalar için diğer ektopik gebeliklere göre daha geç rüptüre olduğu bildirilmiştir. Ciddi kanama riskli mevcuttur. Miyometrium takabasının 5 mm altında görülmesi, endometrial

kavitenin en lateral kısmından 1 cm daha uzak mesafede gebeliğin olması gibi durumlar interstisyel gebelik için tanıda kolaylık sağlamaktadır. Cerrahi yönetimde kornual rezeksiyon veya kornuostomi yapılabilir. Cerrahın deneyimine göre laparoskopik veya laparatomi uygulanabilir. Erken tanı durumunda metotreksat uygulanabileceği bildirilmiş ancak düşük vaka sayısı nedeniyle net bir protokol mevcut değildir (Jermy,2004&Zuo,2012).

Abdominal Gebelik

Tanım olarak abdominal gebelik tubal, overyan veya intraligamenter implantasyondan ayrı olarak periton boşluğunda bir gebeliğin varlığıdır. Ektopik gebelikler arasında nadir görülen bir gebelik türüdür. Gebelik ürünü peritona implante olabildiği gibi bu ektopik gebelik türünde genellikle erken tubal rüptüre veya düşükten sonra meydana geldiği düşünülmektedir. Büyümüş ektopik gebelik olgularında plasentanın peritona yapışması izlenebilir. Tanı koymak oldukça zordur çünkü tam bir ektopik gebeliğe ait semptomlar her zaman görülemeyebilir. Labaratuar testleri genellikle tam bilgi vermeyebilir. Ultrason ile her zaman tanı koymak kolay olmayabilir. Uterustan ayrı izlenen fetüs ve uterus dışında görülen plasental dokular tanıyı koymada yardımcıdır. MR tanı doğrulamak için kullanılabilir (Sherer, 2007&Worley, 2008).

Abdominal gebelik yaşamı tehdit edici bir noktaya gelebildiği bildirilmiştir.Yönetiminde anne yaşı da çok önemlidir. Bazı çalışmalarda fetal viabiliyete sınırına kadar takip edilebileceği bildirilmesine rağmen tam bir görüş birliği mevcut değildir. Abdominal gebelikte yaklaşık %20 oranında fetal malformasyon olduğu gözlenmiş olup bunlardan en sık ekstremite anomalileri ve sinir sistemi anomalileri olduğu gösterilmiştir. Konservativ tedavi

yönteminde ani ve yaşamı tehdit edene batın içi riskin olduğu hasta ile ayrıntılı olarak konuşulmalıdır. Genel görüş ise abdominal gebelik varlığında gebeliğin sonladırılması yönündedir. Cerrahi olarak fetusun doğurtulması ve plasentanın çıkarılmasıdır. Plasenta etrafında yaygın damarlanma mevcut olduğu için gereksiz eksplorasyondan uzak durulmalıdır. Multidisipliner yaklaşım ve üçüncü basamak merkezlerde tedavisi en uygun olandır. Plasentanın kanama riski sebebiyle yerinde bırakıldığı vakalarda ise apse oluşumu tekrar kanama gibi durumlarında geliştiği bildirilmiştir. Plasentanın yerinde bırakıldığı olgularda metotreksat kullanımı ise tartışmalıdır (Martin,1998& Costa,1991&Mittal, 2012).

İntraligamentöz Ektopik Gebelik

Gebelik ürünü mezosalpenkse doğru implantasyon gerçekleşirse rüptür, tubanın peritonla örtülü olmayan kısmında gerçekleşir. Fetal yapı broad ligamenti yaprakları arasında olan boşluğa doğru atılır ve intraligamentöz veya broad ligamenti gebeliği dediğimiz durum gelişir. Yönetim olarak abdominal ektopik gebelikte olan durum gibi yönetilebilir. Bu ektopik gebelik türü son derece nadir görülmektedir. Çoğu olgu laparatomi gerektirirken çok erken gerçekleşen vakalarda laparoskopik cerrahi ile tedavi edilebileceği bildirilmiştir(Cormio, 2006& Seckin, 2011).

Overyan Ektopik Gebelik

Fertilize ovumun overe ektopik olarak implantasyonu son derece nadir görülen bir durumdur. Overyan ektopik gebelik diyebilmek için 4 kriter ile tanımlanmıştır. Aynı taraf tubanın sağlam ve tam olarak görülebiliyor olması, dış gebeliğin overe yerleşmiş olması, dış gebelik ürünün uteroovaryanligament ile bağlantısının olması, over yapısının ortasında plasental dokusunun histolojik

olarak gösterilmesidir. Şikayetleri genellikle tubal ektopik gebelikle benzerdir. Tubal ektopik gebelik kadar erken rüptür izlenmese de rüptür bazen erken dönemde görülebilmektedir. Transvajinal usg ile rüptüre olmamış ektopik gebelikler daha erken dönemde tanınabilmektedir. Yönetimi ise genellikle cerrahidir. Küçük ektopik gebelik ürünleri için kama rezeksiyon veya kistektomidir. Büyük geniş vakalarda ise yönetim ooferektomidir. Küçük ektopik gebeliklerde metotreksat kullanımı ile olumlu sonuçlar da elde edilmiştir. Tedavi sonrası beta-hcg takibi ile persistan trofoplastı dışlamak gereklidir (Comstock,2005&Hassan,2012& Pagidas,2013).

Servikal Gebelik

Servikal gebelik medikal veya cerrahi olarak tedavi edilen bir ektopik gebelik türüdür. Stabil ve erken hafta ektopik gebeliklerde ilk basamak tedavi metotreksat uygulamasıdır. İlacın direk keseye uygulanması veya sistemik uygulanması mümkündür.Medikal tedavi ile birlikte uterin arter embolizasyonu kombinasyonunda kanama açısından son derece faydalı olduğu gösterilmiştir. Servikal gebelikte hasta seçimi son derece önemlidir. Beta-hcg değerinin 10,000mUI üzerinde olması, CRL>10mm üzerinde olması ve fetal aktivite varlığında sistemik metotreksatın başarı şansı düşmektedir. Bu durumda intrakardiyak potasyum klorid uygulanması yapılabilmektedir. Konservativ tedaviler yanında vakum küretaj ve histerektomi de yapılabilir. Kanamanın çok olduğu ve durdurulamadığı vakalarda histerektomi planlanmalıdır. Vakum küretaj öncesinde uterin arter embolizasyonu gibi işlemlerin uygulanması durumunda kanamanın azaldığı bildirilmiştir(Ginsbung, 1994& Jeng, 2007& Zakariya, 2011).

Sezeryan Skar Gebeliği

Sezeryan doğum skarının myometriuma implantasyonu ile gelişir. Sezeryan oranın artması ile birlikte daha fazla görülmekte olup genellikle insindası 2000 gebelikte 1 görülmektedir. Şiddetli kanama bu ektopik gebelik türünde görülebilmekte olup plasenta increata vakaları gibi şiddetli kanadığı bildirilmiştir. Bu ektopik gebelik ağrı ve kanama ile erken bulgu vermektedir. Yaklaşık %40 oranında ise asemptomatik olup rutin ultrason ile yakalanmaktadır. Transvajinal usg tanıda en sık kullanılan yöntem olup şüpheli durumlarda MR gibi görüntüleme yöntemleri kullanılabilir. Tedavi de çeşitli seçenekler mevcuttur. Gebelik düşünmeyen kadınlarda histerektomi planlanabilir. Fertilite koruyucu yöntemler ise konservativ yöntemlerle birlikte metotreksatın lokal ve sistemik uygulamasını içerir. Cerrahi yöntemler ise vakum küretaj, histereskopik rezeksiyon veya istmik rezeksiyon ve histerektomidir. Bu tedavilerin yanında metotreksat uygulaması genellikle birlikte uygulanmaktadır (Rotas, 2006&Timor-Tristch 2012&Shen, 2023).

Nadir Görülen Diğer Ektopik Gebelik Bölgeleri

Dış gebelikler bu anlatılan bölgeler dışında bir çok bölgede daha görüldüğü ancak çok nadir olduğu bildirilmiştir. Omentum, dalak, karaciğer, retroperiton gibi vücudun çok farklı yerlerinde görüldüğü vaka sunumlarında gösterilmiştir.Geçirilmiş uterin cerrahi veya yardımcı üreme teknikleri uygulanan kadınlarda çok nadir de olsa intramural implantasyonların varlığı gösterilmiştir. Abdominal gebeliklerde genellikle laparatomi planlanmakta iken nadir seçili vakalarda hemodinami stabil ise laparoskopik olarak tedavi edilebileceği gösterilmiştir Chin, 2010&Wu, 2013).

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CHAPTER VII

Gebelik ve Bağ Doku Hastalıkları

İhsan ŞAFAK

Giriş

Kollajen bağ doku hastalıklarının asıl önemli iki temel sebebi vardır. Bunlardan birincisi otoantikor ilişkili immün sistem hastalıklardır. Bağ doku hastalıklarında belirli organ ve sistemlerde immün komplekslerin birikmesi nedeniyle hasar meydana gelmektedir. Genellikle cilt tabakasında, eklem bölgesinde, kan damarlarında ve böbreklerde inflamasyona neden olduğu için romatizmal hastalık olarak da değerlendirilmektedir. Bu hastalıklar içinde sistemik lupus eritematozus,romatoid artrit gibi hastalıklar bulunmaktadır. İkinci temel neden ise kemik,kıkırdak, kan damarı, cilt ve bazal membranın kalıtsal hastalıklarıdır. Bu kalıtsal hastalıklar arasında ise marfan sendromu, Ehlers- Danlos sendromu gibi hastalıklar en çok bilinen kalıtsal hastalıklardır. Bağ doku hastalıklarını **Tablo 1** de gösterilen başlıklar altında ayrıntılı olarak ele alacağız (Tepeli, 2017).

Tablo 1: *Bağ doku hastalıkları*

İmmün sistemli bağ doku hastalıkları	Sistemik lupus Eritematozus, Antifosfolipit antikor sendromu, Romatoid artrit, Sistemik skleroz, Vaskülit sendromları, İnflamatuar miyopatiler
Kalıtsal bağ doku hastalıkları	Marfan Sendromu, Ehlers-Danlos Sendromu, Osteogenezis İmperfekta

İmmün nedene bağlı olan bağ doku hastalıkları otoantikor oluşumu ile ilişkili olup olmamasına bağlı olarak ikiye ayrılmaktadır. Romatoid faktör (RF) vücutta bulunan bir otoantikordur. Sistemik lupus eritematozus, romatoid artrit, mikst tip bağ doku hastalığı, skleroderma, vaskülitler gibi çok sayıda otoimmün hastalıkta romatoid faktör pozitif bulunmaktadır. Gebelikte oluşan immünsüprese durum nedeniyle bu hastalıkların bazılarında etkinliğinde azalma olduğu görülmüştür. Gebelik hormonları immün hücrelerde değişikliğe yol açar. Östrojen T hücrelerinin cevabını artırırken androjen azalttığı görülmüştür. Progesteron ise immün sistemi baskılayıcı etkisi mevcuttur (Cutolo,2006& Robinson, 2012).

İmmün sistem nedenli bazı hastalıkların gebeliğe bağlı oluştuğu da gözlenmiştir. Fetal hücrelerin ve fetal DNA'nın maternal kanda bulunması gebelik sonrası dönemde organlarda ve kanda bulunmaya devam etmesine bağlı olarak otoantikorların stimülasyonuna sebep olur. Otoimmün tiroidit ve sistemik sklerozisi olan kadınların dokularında fetal hücreler bulunmuş olup gebeliğe bağlı geliştiği gösterilmiştir. Fetusa geçen maternal hücrelerin de bebekte otoimmün hastalıklara yol açabileceği gösterilmiştir (Lissauer,2009& Ye, 2012).

Sistemik Lupus Eritematozus

Çevresel faktörler ile kişinin genetik olarak duyarlı genlerinin etkileşimi sonucu oluşan kompleks bir patogenizi olan, hetorojen bir immün sistem hastalığıdır. İmmün sistemde etkileşime bağlı olarak otoantikor aktivasyonu ve aşırı B lenfosit aktivitesine sekonder gelişir. Otoantikorların hücresel nükleer alana yönelmesi sonucu hücre hasarı ve sonuçta doku hasarı gerçekleşir. Lupus olgularının yaklaşık %90'ı kadın hastalardır. Gebelik sırasında bir miktar daha fazla görüldüğü bildirilmiştir. Ölümlerin çoğu end-organ hasarı, hipertansiyon, enfeksiyonlar, serebrovasküler hastalıklar ve kardiyovasküler sistem hastalıklarına sekonder gelişmektedir. **Tablo 2'**de sistemik lupu eritematozusun klinik bulguları gösterilmiştir (Tsokos, 2011& Hahn,2012).

***Tablo 2**: Sistemik lupus eritematozusa bağlı şikayetler*

Sistemik şikayetler	Yorgunluk, halsizlik, ateş, kilo kaybı
Kas-iskelet sistemi şikayetleri	Artarji, miyalji,miyopati, poliartrit
Dermatolojik şikayetler	Malar döküntü, diskoid döküntüler, oral ülserler,saç dökülmesi, cilt döküntüleri
Nörolojik şikayetler	Duygu durum bozuklukları, baş ağrısı, nöbet, bilişsel bozukluklar
Hematolojik	Anemi, lökopeni, trombositopeni,splenomegali
Üriner sisteme ait şikayetler	Proteinüri, nefrotik ve nefritik sendrom, böbrek yetmezliği
Gastrointestinal sisteme ait şikayetler	İştahsızlık, bulantı, ağrı, ishal
Oküler şikayetler	Konjoktivit
Kardiyopulmoner	Perikardit,miyokardit,pnömonit

Sistemik lupu eritematozusun klinik bulguları çok değişkenlik göstermektedir. Bazı hastalarda tek organ tutulumu ve ona ait semptomlar mevcut iken bazı durumlarda multisistem organ tutulumu görülmektedir. Ateş, artrit, kızarıklık, perkardit, ışığa hassasiyet, anemi, bilişsel bozukluklar diğer semptomlara göre daha fazla görüldüğü gösterilmiştir. Özellikle SLE'in hafıza ve bilişsel fonksiyonlara olumsuz yönde etkisi kanıtlanmıştır (Kozora,2011).

Antinükleer antikor(ANA) pozitifliği en iyi tarama testi olmakta birlikte pozitif olması durumunda sadece SLE değil başka otoimmün hastalıklarda, viral enfeksiyonlara bağlı olarak da yüksekliği mevcut olup ayırıcı tanıda dikkatli olunmalıdır. Çift sarmallı DNA ve Smith antijenlerine karşı gelişen antikorlar ise görece olarak daha yüksek özgüllüğe sahiptir. Bu hastalık için yüzlerce otoantikor varlığı olmasına rağmen sadece birkaç otoantikor varlığı organ hasarına sebep olmaktadır (Lin 2020).

Sistemik lupus eritematozus ile birlikte gebelik sonuçları son 10 yılda olumlu yönde gelişme göstermiştir. Gebelik sonuçları için önemli faktörler gebeliğin başında hastalığın aktif olup olmaması, yaş, gebelik sayısı, medikal veya obstretrik hastalıklar ile antifosfolipit antikorunun pozitif olup olmaması çok etkilidir. Gebelik sırasında yeni tanı alan lupusun şiddetli olma durumu diğerlerine göre daha fazladır. Gebelik sırasında lupus vakalarının 1/3 kadarı kendiliğinden iyileştiği gözlenmiş olup yine 1/3 kadarı ise kötüleşmiştir. Bu yüzden gebelik sırasında lupus hastalığında artış olabilir veya hiçbir şikayeti olmadan sessiz de seyredebileceği bildirilmiştir. Lupus hem anne hem bebeğin sağlığını tehdit edecek kadar ciddi bir durum olmakla birlikte gebelik öncesi sessiz dönemde olması, protein atılımı veya böbrek tutulumunun

olmaması, antifosfolipid sendrom varlığı olmaması durumunda gebelik sonuçları son derece olumludur (Peart, 2014& Hamed, 2018).

Gebelik sonuçlarına etkisi açısından aktif lupus nefritinde maalesef sonuçlar kötü gebelik sonuçları ile ilişkilidir. Böbrek hastalığı olan hastalarda preeklampsi ve gestasyonel hipertansiyon daha fazla gözlendiği bildirilmiştir. Remisyonda ise sonuçlar daha iyi olduğu gözlenmiştir. Gebelik sırasında lupus nefriti için immünsüpresif tedaviye devam edilmesi önerilmiştir. Ancak doz ile ilgili yeterli veri mevcut değildir. **Tablo 3** de lupusa bağlı olarak gelişen komplikasyonlar göstermiştir. SLE olan hastaların yaklaşık %30 kadarında kronik hipertansiyon ile komplike olduğu bildirilmiştir. Bu hastalarda preeklampsi ve süperempoze preeklampsi sıklığı daha fazla görülmüştür. Böbrek tutulumu dışında başka organ tutulumu yoksa lupusu preeklampsiden ayırmak son derece zordur (Petri, 2007 & Clowse,2008& Stojan, 2012).

Tablo 3: *Sistemik lupus eritematozuslu hastaların gebeliklerinde gelişen komplikasyonlar*

Eşlik eden hastalıklar	-Pregestasyonel diyabet, -Trombofili, -Hipertansiyon, -Böbrek yetmezliği, -Pulmoner hipertansiyon
Gebelik komplikasyonları	Preeklampsi Preterm eylem Fetal büyüme kısıtlılığı Eklampsi
Medikal komplikasyonlar	Anemi Trombositopeni Pulmoner emboli
Enfeksiyonlar	Pnömoni Sepsis

Gebelik sırasında lupus yönetimi oldukça zor olmakta birlikte klinik, laboratuvar ve fetal iyilik halinin takibi ile yapılmaktadır. Gebeliğe bağlı gelişen trompositopeni ve proteinüri lupusa bağlı da gerçekleşebilmektedir yine palmar eritem gebeliğe bağlı olmakla birlikte lupusta da görülebilmekte olup bu durum ayırıcı tanıyı zorlaştırmaktadır. Bazı kliniklerde SLE gebelik skalası kullanılmakta olup bu skala lupusun aktivitesinin şiddetini göstermektedir. Seri olarak yapılan kan tetkikleri, hastalıkta değişiklik olup olmadığı açından faydalı olduğu bildirilmiştir. Pozitif indirek coombs testi, anemi, hemoliz, indirekt hiperbilirubinemi ile birlikteliği mevcuttur. Serum transamilaz aktivitesinde artış karaciğer tutulumu açısından anlamlıdır. Proteinüri değerlendirilmesi açısından sık idrar tahlili önerilmekte olup atılımın artması durumunda kötüye işaret olmakla beraber anormal kreatinin artışı durumunda çok daha dikkatli olunmalıdır. Fetal büyüme kısıtlılığı ve oligohidroamnios açısından yakın takip önerilmektedir (Lateef ,2017&Ruiz-Irastorza, 2020) .

Gebelikte tam olarak bir tedavisi yoktur tam bir remisyon nadir görülmektedir. Bu hastalık hastaların yaklaşık 1/3 ünde hafif seyretmekte olup yaşamı tehdit etmez ancak hastada oluşan ağrı ve yorgunluk hastanın yaşam konforunu bozmaktadır. Düşük doz aspirin kullanılması önerilmektedir. Hastalığı şiddetli geçiren hastalarda düşük doz (1-2mg/kg) oral prednizon gibi ajanlar kullanılabilmektedir. Ancak kullanımı ile birlikte gestasyonel diyabete yatkınlık gelişebilmektedir. Yine diğer ajanlara göre güvenli sayılan Azotioprin gibi ajanlar aktif hastalığı kontrol amaçlı kullanılabilmekte olup gebelikte güvenli olduğu gösterilmiştir. Bazı durumlarda ise mikofenolat aktif hastalığı kontrol için tek ajan olup bu durumda gebelik açısından danışmanlık verilmesi gereklidir.

Şiddetli hastalık durumunda ise yüksek doz kortikosteroid verilmesi gereklidir. Antimalaryel ajanlar ise cilt semptomlarını kontrol için kullanılmakta olup bu ajanlar plasentayı geçtiği gösterilmiş ama konjenital anomali ile ilişkisi bulunmamıştır(Petri, 2006& Hahn, 2012& Briggs, 2015).

Lupus ile komplike olan gebeliklerde kötü gebelik sonuçları ile karşılaşma ihtimali daha fazla olduğu bildirilmiştir. Bu kötü gebelik sonuçları, preterm eylem, fetal büyüme kısıtlılığı, yenidoğan lupus sendromu ve ölü doğumdur. Lupus alevlenmesinde hipertansiyon, proteinüri gibi durumların varlığı kötü prognostik belirteçtir. Korunma yöntemi olarak sistemik lupus eritematozis hastalığı olan kadınlar çocuk sayısında kısıtlamaya gitmek istemektedir. Korunma yöntemi olarak sadece progestin içeren prepartların kullanımı önerilmektedir. Rahim içi araçlar kullanılmasında engel olmamasına rağmen,immünsüpresif tedaviye sekonder enfeksiyon riskinde artış olduğuna dair bilgiler, kanıta dayalı olmayıp kullanılmasında engel yoktur. Tubal sterilizasyon ise sessiz dönemde planlanması ile uygun bir korunma yöntemidir(Chabbert-Buffet,2011&Bramham ,2012)

Antifosfolipid Antikor Sendromu

Fosfolipidler hücre membranın temel bileşenlerindendir. Antifosfolipid antikorlar ise bu fosfolipid yapısına karşı oluşmuş antikorlardır. Bu otoantikorları oluşmasına neden olan mekanizma ise tam olarak net değildir. Daha önce geçirilen enfeksiyonlara sekonder olarak geliştiği düşünülmektedir. Antifosfolipid sendromu, kompleman aktivasyonunun gelişmesine, antikoagülanların inaktive olmasına, prokoagülanların aktive olması ile karakterizedir. Klinik olarak venöz ve arteriyel tromboz, gebelik kayıpları izlenmektedir.

Antifosfolipid sendromunda görülen klinik belirtiler **Tablo 4** de gösterilmiştir (Tsokos,2020& Moutsopoulos,2021).

***Tablo 4**: Antifosfolipid sendromda görülen bulgular*

Arteriyel tromboz	Geçici iskemik atak, inme, miyokard iskemisi
Venöz tromboz	Tromboembolizm, Tromboflebit, livedo retikülaris
Hematolojik	Otoimmün anemi, trombositopeni
Gebelik	Tekrarlayan gebelik kaybı, fetal kayıp, preeklampsi
Diğer	Migren, baş ağrısı, epilepsi,artrit,

Tablo 4 de belirtilen sınıflama tarama endikasyonlarını içerir. Bu sendromun tanısı klinik ile birlikte laboratuvar tetkikleri ile birlikte konulmaktadır. Tanıda öncelikle vasküler tromboz veya gebelik morbiditesinden biri olmalıdır. Bu durumların yanında laboratuvar testlerinden birinin 3 ay arayla iki kez pozitif olması ile tanı kesinleştirilir. Lupus antikoagülan aktivitesinin olması veya yüksek pozitifliği olan spesifik Ig M ve Ig G antikardiyolipin varlığı laboratuvar testlerinin pozitif olduğunun göstergesidir (Miyakis, 2006).

Gebelikte yüksek düzeyde antikardiyolipin antikor varlığında ve bunun yanında lupus antikoagülanı saptanırsa; plasental infarktüse yatkınlık, preeklampsi, fetal büyüme kısıtlılığı, vaskülopati, fetal kayıp gibi olumsuz durumların gelişme ihtimali daha da artmaktadır. Bunların yanında trombositopeni, anemi ve tromboza yatkınlığın da arttığı bildirilmiştir (Clowse, 2008).

Gebelikte bu antikorların oluşması ile ilgili tam patofizyoloji net olmamakla birlikte multifaktöriyeldir. Trombositler otoantikorların etkisi ile hasara uğramaktadır. Otoantikorlar ayrıca hücre membranında bulunan fosfolipid yapısına da saldırarak hücre

hasarına ve sonuç olarak doku hasarına sebep olmaktadır. Antifosfolipid sendrom sonucu gelişen hasar sadece tromboz ile açıklanamamakta olup bunun yanında inflamasyona bağlı hasar da mevcuttur. Antifosfolipid antikor sendromuna sekonder fetal kayıp oranlarında artış olduğu bildirilmiştir. İlk trimester gebelik kayıpları ile daha yakından ilgisi olduğu bildirilmiştir. Yüksek otoantikor titresine sahip kadınlar, düşük titreye sahip kadınlara göre daha olumsuz durumlarla karşılaşma ihtimali fazladır(Nodler, 2009& Tsokos, 2024).

Günümüzde tedavide farklı görüşler olması bazen kafa karıştırıcı olabilmektedir. Yüksek titrede otoantikor varlığı önemli iken düşük titrede ise sadece şüphe uyandırmaktadır. Emboli öyküsü olan, otoantikor yüksekliği olan gebelerin bir sonraki gebeliğinde de bu durumu yaşama ihtimali olduğu için gebelik boyunca heparin ve postpartum en az 6 hafta antikoagülan verilmesi önerilmektedir. Tromboemboli öyküsü olmayan ancak antifosfolipid otoantikor yüksekliği olan ve fetal kayıpları olan hastalara gebelik boyunca antikoagülan tedavi verilmesi önerilen klinikler mevcuttur. Bu tedavi sonrası gebelik kayıpları açısından faydalı olduğuna dair yayınlar mevcuttur. Antifosfolipid antikor sendromu olan ancak tromboemboli öyküsü olmayan durumlarda aspirin gibi ilaçların kullanımını öneren yayınlar mevcuttur. Düşük doz aspirin (60-80 mg) prostoglandin üretimini korurken tromboksan A2 oluşumunu engeller. Prostosiklinlerin ise korunmasını sağlamaktadır. Cerrahi işlemlerin olması durumunda hafif kanama riskini artması dışında önemli bir yan etkisi bildirilmemiştir (Branch, 2010& Del Ross,2013).

Unfraksiyone heparin subkutan olarak 12 saat arayla 5000-10000 ünite arasında verilmesi önerilmekle birlikte genellikle kullanımın kolay olması, trombositopeni riskinin daha az olması nedeniyle günde bir kez yaklaşık 40 mg gibi düşük doz enoksaparin subkutan uygulanmaktadır. Heparin tedavisinin nedeni tromboz oluşmasını engellemek içindir. Heparin otoantikorların yüzeye bağlanmasını engelleyerek hücre hasarını engeller. Glikokortikosteroidler antifosfolipid antikor sendromunda eğer bağ dokuda bir hastalık yok ise gebelikte kullanımı önerilmemektedir. Eğer bunun yanında sistemik lupus eritematozus gelişirse kortikosteroid kullanılması önerilmektedir. İmmünoglobün tedavisi ise şiddetli hastalığı olup heparinin trombositopeni yapması nedeniyle kullanılamadığı durumda önerilmektedir(Carbone,1999& Tsokos,2011&Alijotas-Reig, 2013)

İmmünsüpresif tedavinin etkinliği, gebelikte riskleri de göz önünde bulundurularak kullanımı için net bir durum söz konusu değildir. Azatiopirin ve siklosporinin diğer standart tedavinin yanında kullanılmasının faydası olduğu gösterilmiştir. Aspirin ile birlikte heparinin kullanılması en etkili tedavi yöntemi olarak şu an gösterilmektedir. Daha önce tromboemboli öyküsü olan hastalarda aspirin kullanılmakla birlikte etkinlik açısından yararı kesin değildir. Antifosfolipid antikorları olan hastada eğer tedavi uygulanmaz ise gebelik kayıpları sık görülmektedir. Tedaviye rağmen yine de gebelik kayıp oranı yaklaşık %20 kadar olduğu bildirilmiştir(Ernest,2011&Bouvier, 2014) .

Romatoid Artrit

İmmünolojik nedenli bir patogenizi olan bu hastalığın nedeni tam olarak bilinmemekte olup kronik bir multisistem hastalığıdır.

İnflamasyona ve sistemik birçok semptomun gelişmesine neden olur. En çok periferik eklem bölgelerinde tutulum ile seyretmektedir. Kıkırdak hasarı, eklemlerde deformasyonun gelişimi ve kemik erozyonları oluşumuna sebep olduğu bildirilmiştir. Bu hastalığın genetik yatkınlığının olduğu gösterilmiştir. Sigara içmenin romatoid artrit oluşumu için yatkınlık sağladığı gösterilmiştir (Papadopoulos,2005& Shah,2012).

Tedavide amaç, ağrısın giderilmesi, inflamasyonun azaltılması, eklem fonksiyonlarının devamını sağlamaktır. Aspirin ve nonsteroid antiiflamatuar ilaçların kullanımı tedavide asıl kullanılan ilaçlardır. Ancak bu ilaçların en çok görülen yan etkisi kanamalı gastritin gelişmesidir. Gebelikte ilk trimesterde nonsteroid kullanan hastaların bebeklerinde daha fazla kardiyak anomali geliştiği bildirilmiştir. Ayrıca spontan düşükler ve fetüste pulmoner hipertansiyon ile de ilişkisi bulunmuştur.Tedavi de nonsteroid antiiflamatuar ilaçların yanında glikokortikosteroid ilaçlarında kullanımı hastanın semptomlarını ciddi şekilde azalttığı gösterilmiş olup kullanılması önerilmektedir. Sülfazalin ve hidroksiklorin gibi romatoid artrit için kullanılan ilaçlar gebelikte güvenli olduğu gösterilmiştir. Azatiopirin gibi ilaçlar ise bu ilaçlarla kontrol altına alınamayan şiddetli vakalarda gebelikte kullanılabileceği bildirilmiştir (Briggs ,2011&Briggs,2013).

Gebelik sırasında romatoid artritli hastaların yaklaşık %90 kadarının iyileştiği gösterilmiştir. Hayvan çalışmalarında bu durum incelenmiş olup bunun nedeni olarak gebelikte T hücrelerde değişikliğe sekonder geliştiği düşünülmektedir. Ancak gebelik sonrası alevlenmeler çok daha şiddetlendiği ve sıklaştığı gösterilmiştir. Bunun nedeni postpartum immün sistemde

değişikliklere sekonder alevlenmelerin olduğu düşünülmektedir. Emziren annelerde bu durum daha fazla görülmektedir. Kadınlarda gebelik sonrası hastalığın iyileştiği ve hastalığa karşı gebeliğin koruyucu olduğunu bildiren çalışmalar mevcuttur. Bu iyileşmenin nedeni olarak anne ve fetüs arasında HLA antijenlerindeki değişikliğe sekonder bir iyileşmenin olabileceği düşünülmektedir (Ostensen,2007&Förger,2008).

Gebelik sırasında semptomatik olan romatoid artrit hastalarınının tedavisinde aspirin ve nonsteroid antiiflamatuar ilaçlar kullanılmaktadır. Eğer bunların dışında semptomları kontrol etmek için gerekli ise glikokortikosteroidlerin kullanımı da uygundur. Nonsteroid antiinflamatuar ilaç kullanımı ile duktus arteriozusun erken kapanması, pulmoner sistemde oluşabilecek durumlarla ilgili riskler mevcuttur. Yapılan bir çalışmada ilk trimesterde bu ilaçların kullanımı varlığında yaklaşık %75 bebek sağlıklı olarak doğmuştur. Korunma açısından ise herhangi bir kısıtlama olmayıp romatoid artriti olan hastalar tüm korunma yöntemlerini kullanabilir (Almarzouqi, 2007& Briggs , 2011).

Sistemik Skleroz(Skleroderma)

Tam olarak etyolojisi bilinmeyen kronik, multisistemleri etkileyen hastalıktır. Bu hastalık mikrovasküler hasar, immün sistem aktivasyonu, akciğerde ve böbreklerde kollajen birikimi ile karakterizedir. Normal kollajenin aşırı üretimi hastalığın en önemli özelliğidir. Bazı formları daha hafif seyretmekte ve sadece cillte kollajen birikimi gözlenmektedir. Daha ağır formlarıda ise gastrointestinal sistemde, pulmoner sistemde birikimler gözlenir. Bu hastaların çok büyük bir kısmında antinükleer otoantikorlar izlenir ve immün sistemde yetmezlik görülmektedir. En sık görülen

semptomu soğuk havanın tetiklediği parmaklarda iskemi ve yüzde şişmelerin izlendiği raynould fenomenidir. Sklerodermanın tam olarak tedavisi olmasa da organ tutulumuna yönelik yapılan tedavi ile semptomlar ciddi anlamda düzelmektedir. Bu hastalığın tedavisinde hidroksiklorokin ve düşük doz kortikosteroidler tedavi de yararlıdır. İmmünoglobünler ise perikardit ve anemi varlığında çok etkili değildir. Hastalığa bağlı olarak gelişen pulmoner hipertansiyon varlığında ise mortalite ciddi oranda artmaktadır(Spinillo,2008&Buhimschi,2009&Varga, 2012).

Gebelikte sistemik sklerozis çok düşük bir prevelansa sahiptir. Temel fonksiyonlarında bir problem olmadığı zaman genellikle bu hastalık gebelikte sakin devam etmektedir. Özellikle disfaji ve reflü gebelikte artan şikayetlerden biridir. Özofagusta kas disfonksiyonuna sekonder motilite kaybına bağlı yakınmalar görülmektedir. Normal doğuma engel durum yoktur ancak sklerodermaya bağlı yumuşak dokularda kalınlaşma gerçekleşmiş ise normal doğum önerilmemektedir(Steen, 1999&Gayed,2007).

Sistemik sklerozisi olan hastalar gebe kaldığında gebelik sonuçlarını etkileyen en önemli durum hastalığın şiddetidir. Yapılan çalışmalar incelendiğinde preterm doğum oranında artış, fetal büyüme kısıtlılığı ve fetal ölümlerde de artış olduğu gösterilmiştir(Taraboreli, 2012& Betelli,2018).

Skleroderması olan hastalar için her korunma yöntemi güvenli değildir. Gebelik istemeyen hastalar için oral kontraseptif ilaçların kullanılması önerilmemektedir. Sistemik sklerozis kronik bir hastalık olduğu için gebelik açısından bilgilendirilmeli ve kalıcı korunma yöntemi açısından sterilizasyon detaylı olarak anlatılmalıdır(Bernatsky,2008)

Vaskülit Sendromları

Vaskülitler genel olarak kan damarlarındaki inflamasyonu ve hasarın oluşturduğu hastalıkları ifade etmektedir. Bu hastalıklar genel olarak immün sistemdeki bir bozukluğa bağlı veya immün sistem komplekslerin birikimlerine bağlı geliştiği düşünülmektedir. Vaskülit yapan başlıca hastalıklar, poliarterizis nodosa, Wegener granülamatozusu, dev hücreli arterit, Takayusu arteriti ve Behçet hastalığıdır. Bunların yanında birçok vaskülite neden olan hastalık da mevcuttur(Goodman,2019).

Poliarterizis nodoza

Küçük ve orta büyüklükteki arterlerin vaskülitidir. Bu hastalığa bağlı olarak gastrointestinal yakınmalar, nöropati, hipertansiyon ve üriner sisteme ait özellikle böbrekle ilgili şikayetler görülebilmektedir. Semptomlar genellikle nonspesifiktir. Tanı biyopsi ile netleştirilmektedir. Gebelikle birlikte çok nadir poliarterizis nodosa vakası görülmektedir. Tedavi için yüksek doz glikokortikosteroidler uygulanmaktadır (langford, 2012).

Wegener Granülomatozisi

Bu hastalık böbreğin, solunum sisteminin nekrotizan vaskülitidir. Pulmoner infiltrasyonlar, nodüller, kas iskelet sistemi lezyonları ve glomerülenefritler izlenmektedir. Litaretürde vakalar incelendiğinde Wegener granülomatozisi olan bir gebede 32.haftasında trombotik mikroanjiyopati ve renal sistemde bozukluk geliştiği bildirilmiştir. Tedavi de yine kullanılan en önemli ilaçlar kortikosteroidlerdir. Gebeliğin geç döneminde siklofosfomidlerle kombine kullanımı da mevcuttur(Pagnoux,2011&Kayatas,2012).

Takayasu Arteriti

Bu hastalık nabızsızlık hastalığı olarak da bilinmektedir. Genç hastalarda daha sık görülmektedir. Takayasu arteriti büyük damarları tutar ve kronik inflamatuar bir arterittir. Üst ekstremitelerde vasküler sistemde bozukluklarla seyreder. Ölüm konjektif kalp yetmezliği ve serebravasküler sistemde bozukluklar sonucu genellikle olur. Glikokortikosteroidlere son derece iyi yanıt gelişir ancak tam kür sağlayan bir tedavi yoktur. Tutulan yere bağlı olarak gebelik sonuçları değişir. Abdominal bölge de tutulum olması durumunda gebelik sonuçları son derece kötü seyrettiği bildirilmiştir. Bu vaskülit yapan hastalıkların yanında henoch-Schönlein purpurası, Behçet hastalığı, Churg-Straus vasküliti de bu hastalığa sebep olmaktadır.(Johnston, 2002& Dey, 2015).

İnflamatuar Miyopatiler

İskelet kas güçsüzlüğüne neden olan hastalıklar arasında en çok görülen ve tedavi edilebilen hastalık grubudur. Bu hastalık grubu içinde polimiyozit, dermatomiyozit, inklüzyon miyoziti bulunmaktadır. Bu hastalıkların çoğunda simetrik olmayan bir kas güçsüzlüğü mevcuttur. Bu hastalık grubunda olan hastalıklar otoimmün hastalıklarla, maligniteyle, bağ doku hastalıklarıyla ilişkili olduğu bildirilmiştir. Tedavi protokolünde yüksek doz kortikosteroidler kullanılmaktadır. Bunun yanında immünsüpresif ilaçlarda kullanılmaktadır. Gebelikte de inflamatuar miyopati hasta sayısı son derece az görülmekle birlikte gebe hastalarda gebelik kaybı,preterm doğumlar görülmüştür. Yeteri kadar veri ise mevcut değildir. Yapılan çalışmalar incelendiğinde gebeliğin sonuçlarının hastalığın şiddeti veya yeni başlayıp başlamaması ile ilişkili olduğu gösterilmiştir(Doria, 2004&Dalakas, 2012).

Kalıtsal bağ doku hastalıklarında çok sayıda mutasyon olduğu gösterilmiştir. Kalıtsal bağ doku hastalıklarında Marfan Sendromu, Ehlers-Danlos hastalığı ve osteogenezis imperfekta en bilinen hastalıklardır. Bu hastalıklarda kondroplaziler ve epidermelizis büllosa gibi klinik durumlar gelişebilmektedir. Gebelikte ise asıl korku bu hastalıklarında anevrizma gelişmesine yatkınlık sağlamaktadır(Schoenhoff,2013).

Marfan Sendromu

Bu hastalık en sık görülen otozomal dominant geçişli olan bağ doku hastalığıdır. Her iki cinsiyeti eşit etkilediği bildirilmiştir. 15. kromozomun uzun kolunda gelişen bir mutasyon sonucu gelişmektedir. Bu vakaların birçoğu hafif vakalar olup ağır vakalarda elastikiyet kaybına sekonder olarak aort dilatasyonu gelişebilmektedir. Gebelikte ise anevrizma gelişme riski arttığı gözlenmiştir(Curry, 2014&Pope, 2019) .

Ehlers-Danlos Sendromu

Bu hastalıkta özellikle cilt elastikiyeti daha yaygındır. Şiddetli olgularda ise inme ve kanamaya kadar giden hastanın mortalitesini artıran klinik bulguları mevcuttur. Otozomal dominant ve resesif geçen tipleri mevcuttur. Bazı tipleri özellikte tip 4 Ehlers Danlos sendromunda preterm doğum, arter rüptürü ve uterus rüptürü riskinin arttığı gösterilmiştir. Ehlers Danlos sendromu olan gebelerde postpartum kanama ve erken membran rüptürü daha sık görülmektedir. Dokudaki bozukluk sebebiyle hem sezeryan doğum da hem de normal doğum sonrası epizyotomi onarımı son derece zordur(Bloom, 2010&Wang, 2013).

Osteogenezis İmperfekta

Bu hastalıkta çok düşük kemik kitlesine sahip ve kırılgan bir kemik yapısı varlığı mevcuttur. Hastaların klinik bulgularında çoklu kırık öyküsü, işitme kayıpları, mavi sklera mevcuttur.Çok fazla alt tipi mevcuttur. Tip 1 en hafif formu olup en ağır formu ve ölümcül seyreden formu ise Tip 2 dir. Tip 1 osteogenezis imperfektası olan kadınlar gebe kalma şansı vardır. Ancak gebelik sırasında kemik kırıkları, skolyoz, akciğerde gelişen rahatsızlıklar gelişebilmektedir. Otogenezis imperfektası olan hastalarda genel olarak tedavi kemik kütlesini artırmak ve kemik kaybını azaltmak için uygulanan tedaviler dışında genelde başka bir tedavi uygulanmamaktadır. Kemik kaybını azaltmak için ise genelde bifosfonatlar kullanılmaktadır. Bu hastalığın ise prenatal olarak tanısı mevcuttur(Prockop, 2012&Vorberding,2022).

Kaynakça

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CHAPTER VIII

Ovarian Cancer

Oznur ONER[1]

1.Introduction

Ovarian cancer is the secondly most diagnosed gynecologic malignant tumor, after uterine cancer, in developed countries; while it is the thirdly most diagnosed one in underdeveloped countries, after cervical and uterine cancer (Torre & ark., 2015). It has caused about 325,000 new cases and 207,000 deaths around the world in 2020 (International Agency for Research on Cancer, 2021).

95 percent of the ovarian malignancies are epithelial cancers; while the rest are germ cell tumors and sex cord-stromal tumors (Robboy, 2009). Epithelial ovarian cancer is the main reason of gynecologic cancer mortality, besides the fifth most important reason of woman cancer mortality in the United States (Armstrong & ark., 2021).

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High-grade serous epithelial ovarian carcinoma (EOC), fallopian tube, and peritoneal carcinomas can be noted as one entity because of their common pathogenesis, clinical features and treatment options. Therefore, the term EOC will be used to mention these malignancies.

Tumor grade and stage are the key points for the management of these neoplasms. Since the risk factors, precursor lesions, clinical presentations, spreading patterns and prognosis differ in each clinical entity; it is crucial to make a precise subclassification (Board, 2020).

2. Epithelial ovarian carcinoma

2.1 Histopathology and pathogeneis

Epithelial ovarian carcinomas can be subclassified in five groups according to histopathology, immunohistochemistry and genetic analysis (Lee, 2003) such as; high-grade serous carcinoma (HGSC), endometrioid carcinoma, clear cell carcinomas, mucinous carcinoma and low-grade serous carcinoma (LGSC).

Although HGSC and LGSC are currently acknowledged to be distinct neoplasms due to the difference between their molecular pathogenesis (Singer & ark., 2003); they are both suggested to arise from fallopian tube lesions; HGSC from serous tubal intraepithelial carcinoma, and LGSC from endosalpingiosis/müllerian rests (Jarboe & ark., 2008).

The molecular genetic analysis and the prognoses of the subtypes vary among the subtypes. *TP53* and *BRCA* mutations are normally carried in HGSCs, while *KRAS* and *BRAF* mutations are

more common in LGSCs (Prat & FIGO Committee on Gynecologic Oncology, 2014).

2.1.1 High-grade serous carcinoma

As it consists of nearly 70-80% of all ovarian malignancies, high-grade serous carcinoma (HGSC) is the most prevalent ovarian cancer subtype. The age of patients mostly vary between 45-65 years, with a median age of 57 years (Köbel & ark., 2010). Since the vast majority of the HGSCs are detected at stage III or IV, the prognosis is usually poor. Less than 10% are detected at an early stage when the tumor is restricted to the ovary (Li & ark., 2012).

Macroscopically, HGSCs are usually cystic and multilocular masses that can vary from microscopic to more than 20 cm in size (Kurman, 2013). They commonly have a serous content with papillary projections.

Gross metastases and omental cake are common in HGSCs, whereas in about 25 percent of patients, micro metastases that are hidden in a completely normal appearing omentum are detected (Kurman, 2013).

Microscopically, HGSCs may contain complex papillary, solid, microcystic areas and Psammoma bodies. However, remarkable cytologic atypia with evident mitotic activity is the critical microscopic component. The atypical cells have large, hyperchromatic nuclei. The treshold of the mitotic rate for HGSC is ≥12 mitoses per 10 high-powered fields (HPF) (Li & ark., 2012). Atypical mitotic figures are common.

Immunophenotypically, p53 and p16 expression is typical for HGSC; while WT-1, estrogen receptor, and PAX-8 are also mostly expressed. Ki67 proliferative index is high.

Up to 10 percent of patients with HGSC have *BRCA1* or *BRCA2* germline mutations (Hennessy & ark., 2010). This leads to a 30-50 percent risk of getting diagnosed with ovarian cancer, especially HGCS, until the age of 70. In addition, around 50 to 80 percent of HGSC cases express mutations in tumor protein p53 gene (*TP53*) (Herrington & McCluggage, 2010). Less than 10 percent of the patients express mutations in *PTEN* and *PI3CA* (Willner & ark., 2007).

2.1.2 Low-grade serous carcinoma

Low-grade serous carcinomas (LGSC) are rare and form less than 5 percent of all ovarian cancers. (Gershenson & ark., 2006). Similar to HGSCs, LGSCs are detected at stage III or IV and therefore, the prognosis is usually poor. In contrast to HGSCs, they are slow-developing tumors that are relatively unresponsive to platinum-based chemotherapy (Gershenson & ark., 2009).

Macroscopically, it is usually difficult to differenciate LGSCs from HGSCs and borderline tumors. They may have papillary projections, but necrosis is usually less evident. On the other hand, psammoma body formation is abundant.

Microscopically, LGSC is an invasive carcinoma and stromal invasion is its difference from borderline tumors.

LGSC is distinguished from HGSC by cytologic differences. The neoplastic cells in LGSC have uniform nuclei with smaller size than the ones in HGSC. This uniformity of nuclear size is an

extremely reproducible and distinguishing characteristic of LGSC (Malpica & ark., 2007). The lower mitotic activity with less than 12 mitoses per 10 HPF is also a component used to distinguish LGSC from HGSC.

Hyalinised stroma with abundant psammoma bodies is another evident feature of LGSC.

Furthermore, the peritoneal involvements that were formerly identified as "invasive implant" are now classified as metastases from a LGSC. Therefore, when a serous borderline tumor is shown to have invasive implants, this tumor will be classified as a LGSC and the implants will be identified as metastases (McKenney & ark., 2016).

Although LGSC is immunophenotypically similar to HGSC and serous borderline tumors, it differs from them with low Ki67 proliferation rates and weak p53 expression. LGSCs do not express HNF-1 beta and calretinin, whereas they express WT-1, estrogen receptor, progesterone receptor.

Contrary to the p53 or *BRCA* 1/2 expression in HGSCs; LGSC and serous borderline tumors usually express *BRAF* and *KRAS* mutations (Singer & ark., 2003). Chromosomal instability or common DNA copy alterations are also not evident in LGSCs and serous borderline tumors as in HGSCs (Kuo % ark., 2009).

Based on all these findings, two pathways have been suggested for serous ovarian carcinogenesis. The first pathway consists of *p53* mutations that are prominent in HGSCs, while the second consists of *KRAS* and *BRAF* mutations that are the key features in LGSCs. These studies have also suggested serous

borderline tumors as precursors for LGSC and that LGSCs don't progress into HGSCs (Bodurka & ark., 2012). Since LGSCs are relatively insensitive to platinum-based chemotherapy, these findings may lead to new treatment options such as agents targeting the *KRAS* and *BRAF* pathways.

2.1.3 Endometrioid carcinoma

Ovarian endometrioid carcinoma forms about 10 percent of ovarian carcinomas. The age of patients mostly vary between 40-50 years, with an average of 56 years (Seidman & Kurman, 2003). Contrary to serous carcinomas, endometrioid carcinomas are diagnosed at early stage and therefore, the prognosis is better (Prat, Ribé & Gallardo, 2005). They are relatively chemosensitive and this also helps for a better prognosis.

Primary ovarian endometrioid adenocarcinomas are generally low-grade. On the contrary, high grade endometrioid carcinomas are suggested to be a subtype of HGSC due to morphological and molecular similarities through immunophenotypic and gene profiling studies (Tothill & ark., 2008).

Ovarian endometrioid carcinoma is related to and suggested to emerge from endometriosis and about 42 percent of ovarian endometrioid carcinoma cases have proof of pelvic or ovarian endometriosis simultaneously (Bell, Weinstock & Scully, 1988).

In about 15-20 percent of the patients, ovarian endometrioid carcinoma is associated with endometrial carcinoma (Board, 2020). These tumors are also very similar histologically. In a case of a concurrent endometrial carcinoma and ovarian carcinoma, the highest probability is a primary endometrial carcinoma with a

metastasis to the ovary. However, there is also possibility of an ovarian tumor with a metastasis to the endometrium or concurrent primary tumors of the ovary and endometrium.

Macroscopically, endometrioid carcinoma may be solid or cystic and it usually contains endometriosis foci presenting the typical "chocolate cyst" appearance. The tumor is generally limited to one ovary. Bilateral lesions have a higher probability of metastasis from an endometrial carcinoma.

Endometrioid carcinoma may contain hemorrage and necrosis areas, whereas it doesn't contain papillary projections.

Microscopically, ovarian endometrioid carcinoma has similarities with low-grade endometrioid endometrial carcinoma. Mitotic patterns are common and squamous morules with immature-appearing cells are usually identified. Endometriosis containing endometrial stroma and epithelium is usually identified.

Immunophenotypically, low-grade endometrioid adenocarcinomas resemble endometrioid endometrial carcinomas. They express ER, PR, PAX-8, vimentin and CA 125; whereas there is no expression of WT-1, calretinin, and inhibin. They may focally express p16 and p53 or may be negative for them. However, high-grade endometrioid carcinomas resemble HGSC as they express p53, p16, and WT-1 strongly and diffusely. Therefore, high-grade endometrioid carcinoma is suggested to be a HGSC subtype, but there are still discussions about it. *CTNNB-1* (beta-catenin) and *PTEN* gene mutations are the most widely recognized mutations detected in ovarian endometrioid carcinomas (Catasús & ark., 2004). *PIK3CA* and *ARID1A* mutations are also common (Irving & ark., 2005). Microsatellite instability is also identified in high levels.

Endometrioid carcinoma is the most common ovarian carcinoma subtype which is associated with Lynch syndrome (Gras & ark., 2001).

2.1.4 Clear cell carcinoma

Clear cell carcinoma forms about 5-10 percent of ovarian cancers in America and usually arises in perimenopausal women (Banks, 2001). Clear cell carcinoma accounts for a bigger part of ovarian carcinomas in East Asia, but whether the reason is environmental or genetic factors has not yet been clarified (Sugiyama & ark., 2000).

Ovarian clear cell carcinomas are frequently detected at early stages (stage I or II) similar to endometrioid carcinomas and the prognosis is relatively good. However, the prognosis is worse than serous carcinomas if clear cell carcinomas are detected at advanced stages since they are not so sensitive to platinum-based chemotherapy (Chan & ark., 2008). Clear cell carcinomas are associated with paraneoplastic hypercalcemia and an elevated risk of thrombosis (Jenison & ark., 1989).

Clear cell carcinomas are related to endometriosis and clear cell adenofibromas; besides, they are likely to present from these lesions (Veras & ark., 2009). About 15-20 percent of clear cell carcinomas consist of an evident adenofibromatous component. Tubal ligation is suggested to lower the risk of ovarian clear cell carcinoma, probably by preventing retrograde menstruation and endometriosis (Kurian & ark., 2005).

Macroscopically, an ovarian clear cell carcinoma usually forms a big, thick walled cystic tumoral mass that contains a mucinous or watery liquid with fleshy nodular protrusions.

Microscopically, clear cell carcinomas contain variable histologic forms; mostly solid, papillary and tubulocystic (Seidman & Kurman, 2003).

Clear cell carcinomas usually have an eminent hyalinized stroma. The nuclei of the tumor cells have variable shapes and sizes. Nuclear atypia may appear in varying degrees, whereas regions with evident cytologic atypia are quite common. Mitotic activity is usually lower than the other subtypes of epithelial ovarian carcinomas.

Considering epithelial ovarian carcinomas, the immunophenotype of clear cell carcinomas is exceptional since they don't express estrogen receptors and WT-1. Expression of p53 may occur. The expression of napsin-A, glypican-3, hypoxia-inducible factor 1 alpha (HIF-1 alpha) and hepatocyte nuclear factor 1-beta (HNF-1 beta) is typical (Lee & ark., 2007). Since HNF-1 is expressed in 82-100 percent of clear cell carcinomas and not expressed in the other epithelial ovarian carcinoma subtypes with a few rare exceptions, it may be suggested as a marker with high specifity and sensitivity for clear cell cancers (Kalloger & ark., 2011).

Clear cell carcinomas may express *KRAS*, *PTEN*, and *PIK3CA* mutations (Amemiya & ark., 2004). Clear cell carcinomas are related to Lynch syndrome and they express microsatellite instability and mutations in *ARID1A* (Wiegand & ark., 2010).

2.1.5 Mucinous carcinoma

Mucinous carcinoma forms about 3-4 percent of ovarian cancers and usually arises in perimenopausal patients (Hart & Norris, 1973). Almost all cases are detected at early stages, usually stage I.

A mucinous carcinoma in the ovary is generally a metastasis of a gastrointestinal musinous tumor (Riopel, Ronnett & Kurman, 1999). Primary ovarian mucinous carcinomas are suggested to emerge from mucinous borderline neoplasms since they mostly appear together (Hart & Norris, 1973).

Mucinous carcinomas are usually large masses, sometimes larger than 20 cm (Hoerl & Hart, 1998). They typically present as a unilateral, smooth faced tumor that is confined to one ovary (Hart & Norris, 1973).

Contrary to what was previously thought, pseudomyxoma peritonei does not appear as a result of the rupture of a primary ovarian musinous carcinoma. It usually emerges from metastasis to ovaries, especially from an appendix tumor (Lee & Scully, 2000).

Musinous cell carcinomas contain cells that look like the ones in endoservix, intestine and gastric pylorus. Both musinous cell carcinomas and musinous borderline tumors mostly have gastrointestinal differentiation; and the basic distinction between carcinomas and borderline tumors is the lack of invasion in borderline tumors.

Immunophenotypically, musinous carcinomas usually express CK7 and gastrointestinal markers such as CK 20, CDX2 (McCluggage, 2006). They usually don’t express ER, PR, CA-125

and WT-1, whereas there may be an expression of p16 (Vang & ark., 2006).

More than 75 percent of ovarian musinous carcinomas express *KRAS* mutation and the same mutation is also expressed in mucinous cystadenomas and mucinous borderline neoplasms. This supports the idea that musinous cystadenoma may progress to borderline neoplasm and to carcinoma (Kurman & Shih, 2008). Ovarian mucinous carcinomas also express many mucin genes that are a feature of all mucinous carcinomas from any site (Kurman & Shih, 2008).

2.1.6 Other histologic subtypes

2.1.6.1 Transitional cell carcinoma

Previously, transitional cell carcinomas were defined as neoplasms consisting of epithelial cells that look like urothelium (Cuatrecasas & ark., 2009). Although they were believed to be examples of malignant Brenner tumors, studies have shown that they expressed the same mutations with HGSCs (Logani & ark., 2003). Therefore, they are mostly suggested to be a subtype of HGSC which contains an epithelium that looks like malignant epithelium.

2.1.6.2 Carcinosarcoma

Carcinosarcomas, likewise known as malignant mixed müllerian tumor (MMMT), account for 2-7.5 percent of ovarian carcinomas and often arise at an average age of 75 years (Seidman & Kurman, 2003). They are often detected at advanced stage as a large mass with necrosis and hemorrhage. These neoplasms typically consist of a combination of malignant stromal and epithelial components. The cells of the stromal component have evident atypia and mitotic index, while the epithelial component usually resembles

HGSC. As a result, they behave very aggressively like HGSCs (Mano & ark., 2007).

2.1.6.3 Undifferentiated / dedifferentiated carcinoma

These are rare tumors and they resemble the ones that arise in the uterus. Microscopically, they commonly contain necrosis, high mitotic activity and tumor-infiltrating lymphocytes.

These tumors are highly aggressive and they are generally detected in late stage. Therefore, the prognosis and overall survival are poor (Shih & Kurman, 2004).

2.1.6.4 Borderline neoplasms

In 1970s, bordeline ovarian epithelial neoplasms were defined as neoplasms that didn't have evident malignant characteristics such as invasion, but sometimes had intraperitoneal spread (Seidman & Kurman, 2003). They displayed behavioral features that were between cystadenomas and invasive carcinomas.

Borderline neoplasms form about 14-15 percent of total primary ovarian neoplasms (Skírnisdóttir & ark., 2008).

2.2 Incidence

Ovarian carcinoma: Ovarian cancer is the secondly most diagnosed gynecologic malignant tumor, after uterine cancer, in developed countries; while it is the thirdly most diagnosed one in underdeveloped countries, after cervical and uterine cancer (Torre & ark., 2015). It has caused about 325,000 new cases and 207,000 deaths around the world in 2020 (International Agency for Research on Cancer, 2021).

Fallopian tube carcinoma: These neoplasms are not as rare as they used to be thought. That's because, most ovarian cancers are

recently suggested to originate from the fallopian tube, then extend to the ovary (Berek & ark., 2021).

Peritoneal carcinoma: These neoplasms also used to be believed as rare but the incidence is now supposed to be higher. That's due to the impossibility to distinguish peritoneal carcinoma involving the ovary from stage III ovarian cancer (Berek & ark., 2016).

2.3 Risk factors

Older age: The incidence of epithelial ovarian carcinomas (EOC) increase by age while they arise at an average age of 65 years (Joueidi & ark., 2020). The risk is suggested to increase about 2 percent for each year before 50 years old, whereas the increase is 11 percent for each year after 50 years old (Gates & ark., 2010).

Germ cell tumors prevail in patients younger than 20 yeras old, while borderline tumors predominate in patients between 30-40 years old and EOCs are the predominant group after 50 years (Berek & ark., 2021).

Ovarian cancers arise in younger ages in hereditary cancer syndromes. It has been found to occur at a mean age of 43 and 49 years in two studies including patients with Lynch syndrome (Watson & ark., 2001). In a prospective study, ovarian cancer was detected at an average" age of 54.0 and 59.5 years in patients with *BRCA1* and *BRCA2* mutation, respectively (Kuchenbaecker & ark., 2017)

Early menarche and late menopause: In some studies, early menarche has been shown to increase EOC risk (Tsilidis & ark., 2011). Similarly, late menopause has been found to cause an increase

in EOC risk (Tsilidis & ark., 2011). The mechanism that is suggested to explation this association is that each ovulation year seems to increase EOC risk by 2-7 percent (Gates & ark., 2010). The trauma caused by repeated ovulation to the ovarian epithelium is blamed to trigger carcinogenesis (Salehi & ark., 2008). The lower EOC incidence in patients whose ovulation is supressed by pregnancy, lactation or oral conraceptive use, supports this hypothesis.

Genetic factors: Ovarian cancer risk is suggested to be 5 percent in a case with one first-degree relative with ovarian cancer, 7 percent with two relatives and 3.5 percent with one second-degree relative (Kerlikowske, Brown & Grady, 1992). The reason for this risk may be the genes related to ovarian cancer and Lynch syndrome. Heritable variants are supposed to form about 25 percent of ovarian cancer cases (Wen & ark., 2023).

Nulliparity: Parous people are suggested to have a lower risk due to the lower number of ovulations.

Endometriosis: Endometriosis seems to be related to some EOC subtypes like endometrioid carcinoma and clear cell carcinoma.

Asbestos: In a meta-analysis, asbestos exposure was shown to be related with an increase in EOC mortality (Camargo & ark., 2011).

Pelvic radiation: In a cohort study including 20000 rectal cancer cases, the risk of ovarian cancer was found to be higher in the radiotherapy plus surgery group than the surgery alone group (Guan & ark., 2021).

Cigarette smoking: A systematic review has shown that smoking is related with an increased risk of musinous ovarian cancer (Jordan & ark., 2006). Higher smoking levels resulted with higher cancer risk. In addition, survival rates in ovarian cancer were lower in smokers (Praestegaard & ark., 2017).

Other factors: Alcohol intake has been shown to have no relation with EOC risk (Rota & ark., 2012). However, pelvic inflammatory disease has been found to be related with ovarian cancer (Lin & ark., 2011). In addition, a relation between diabetes and ovarian cancer has been reported (Zhang & ark., 2017).

On the other hand, the protective factors which are mostly related with decreasing ovarian cancer risk may be listed as bilateral salpingo-oophorectomy, oral contraceptive use, parity, breastfeeding, tubal ligation and hysterectomy.

2.4 Clinical symptoms

The symptoms of EOC may be acute, subacute, or it may be detected during examination, imaging studies, or surgery.

Acute presentation: These are usually the patients with advanced disease who need to be managed urgently. The patient may come out with ascites, dyspnea as a result of pleural effusion, nausea and vomiting caused by bowel obstruction or venous thromboembolism.

Subacute presentation: Subacute presentation is more common in EOC and contrary to what had been believed previously, it has been shown that symptoms may emerge even at the early stages (Goff & ark., 2000). Symptoms may be bloating and abdominal distension, pelvic or abdominal pain, urinary urgency or

fequency, nausea, anorexia or vaginal bleeding. Rarely, there may be lymphadenopathy, rectal bleeding or paraneoplastic syndromes such as hemolytic anemia, cerebellar degeneration, nephrotic syndrome or disseminated intravascular coagulation (Shanbhogue & ark., 2010).

Incidental finding: An adnexal mass of EOC may be found incidentally. Similarly, occult EOC may be discovered after surgery on examination of the pathology specimens.

2.5 Diagnostic evaluation

Evaluation of patients with suspected EOC should be done step by step. Initial evalution, which helps to decide whether further evaluation or surgery is needed, consists of physical examination, imaging by pelvic ultrasonography and laboratory studies. If there is a high level of suspicion of cancer as a result of initial evaluation, the patient should be referred to a gynecologic oncologist.

The most important findings that are suggestive for EOC are an adnexal mass containing a solid component usually with papillary projections, thick septations and Doppler demonstration of flow; and ascites.

Cancer antigen 125 (CA 125) is the most commonly used marker in EOC. A baseline level should be determined, since it is evaluated to assess the result of treatment and to detect recurrence (Prat & FIGO Committee on Gynecologic Oncology, 2014). In up to 85 percent of EOC cases, CA 125 will be elevated (González-Martín & ark., 2023). On the other hand, CA 125 levels may also vary with many other conditions such as fibroids, functional ovarian cysts,

endometriosis, body mass index (BMI), cigarette smoking and menstruation.

Other tumor serum biomarkers such as human epididymis protein 4 (HE-4), alpha fetoprotein (AFP), cancer antigen 19-9 (CA 19-9) or carcinoembryonic antigen (CEA) should be ordered when indicated.

HE4 is approved by the FDA for the assessment of recurrence or progression in EOC and may especially be helpful in cases with normal CA 125 levels (Plotti & ark., 2019). In addition, HE4 may help predicting the prognosis as suggested in a study, which has shown that preoperative high HE4 levels were associated with increased mortality (Furrer & ark., 2019). Being affected by pregnancy and age is the major limitation about HE4.

Once the initial evaluation is completed and the probability of cancer is high, subsequent evaluation for metastatic disease should be performed. Therefore, the medical history and physical examination should primarily assess symptoms and findings that are suggestive for metastatic disease. This assessment will help the surgeon choose the best treatment method, such as surgery or neoadjuvant chemotherapy.

Imaging studies, mostly abdominal and pelvic CT or MRI, are performed to assess the spread of the tumor and the presence of ascites. In a study, positron emission tomography has been shown to increase the detection of metastatic EOC when used alone or combined with CT, in comparison to CT alone or MRI (Musto & ark., 2011); however, further studies are needed.

Chest CT is usually used to evaluate mediastinal lymphadenopathy, pulmonary metastases and pleural effusion. Bone and brain scans are not needed if the patient has no findings that are suggestive for metastasis to these sites.

Neoadjuvant chemotherapy (NACT) is preferred to primary surgery in some cases, such as patients with advanced and unresectable disease or patients with a poor health status. In such conditions, a biopsy is required to make a diagnosis before chemotherapy.

Paracentesis or thoracentesis may be used if the patient has ascites or pleural effusion, respectively. Cytologic evaluation is performed in the samples.

Omental or pleural biopsies may be used in patients whose findings are suggestive for omental or pleural metastases. These biopsies may help not only make a diagnosis but also decide management methods (Hewitt & ark., 2007).

Image-guided biopsy of the ovary should not be performed due to the risk of spillage of tumor cells (Mehdi & ark., 2010).

Evaluation also includes surveilling for other cancers. Studies including metastatic neoplasms to the ovary have found the primary tumor site as colon by15-32 percent, breast by 8-28 percent, gastric by 6-22 percent and appendix by 2-20 percent (De Waal & ark., 2009).

Endometrial cancer is the second most likely gynecologic cancer that occurs as an adnexal mass. Therefore, endometrial sampling is necessary in patients who have abnormal uterine bleeding or a uterine mass, before surgery for suspected EOC. In

addition, ovarian and endometrial cancers may also present as synchronous primary cancers.

Diagnostic laparoscopy can be effective for both surgical evaluation and to assess cytoreductive feasibility, especially in patients who have symptoms suggestive for EOC and/or ascites, with elevated tumor markers. However, if laparoscopy is planned, it should be performed by a gynecologic oncologist experienced in laparoscopic assessment of cancer.

2.6 Testing for hereditary cancer syndromes

Genetic risk evaluation should be performed in all EOC patients with ovarian, fallopian tube, or peritoneal cancer, no matter what their family history is (Konstantinopoulos & ark., 2020). Testing for BRCA1 or BRCA2 mutations and familial cancer syndromes, such as Lynch syndrome should be performed in patients with EOC. Similarly, testing for DNA mismatch repair deficiency should be performed in patients with endometrioid, clear cell or mucinous ovarian cancer.

A family history of cancer syndrome may affect treatment, surgical planning and posttreatment care. For instance; response to poly (ADP-ribose) polymerase (PARP) inhibitors is better in patients expressing *BRCA* mutations (Konstantinopoulos & ark., 2020) and synchronous primary cancer risk is higher in cases with Lynch syndrome.

2.7 Referral to a specialist

Staging and cytoreduction by a gynecologic oncologist has been proven to improve prognosis in EOC. Therefore, patients should be referred to a a gynecologic oncologist when suspicion of

EOC is high. A guideline about criteria for referral to a gynecologic oncologist has been published by the American College of Obstetricians and Gynecologists (ACOG) and the Society of Gynecologic Oncology (SGO) (American College of Obstetricians and Gynecologists, 2011). According to this guideline, if a patient has a pelvic mass and any of the findings in Table 1, she should be referred.

Table 1: Criteria for referral of a patient with a pelvic mass: ACOG Guidelines

Premenopausal patients
CA 125 levels are very high*
Ascites
Proof of metastasis
Postmenopausal patients
CA 125 levels are high*[2]
Ascites
Fixed or nodular pelvic mass
Proof of metastasis

Reference: American College of Obstetricians and Gynecologists, 2011

In addition, the Risk of Ovarian Cancer Algorithm (ROCA) is a computer algorithm that can be used for the assessment of ovarian cancer risk.

[2] There is no specific value for high CA 125 levels in 2011 guidelines.

Table 2: 8th edition AJCC, FIGO/TNM Staging System for Ovarian Cancer

Stage I	Tumor limited to ovaries (one or two) or fallopian tube(s)
IA	Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on the surface of ovary or fallopian tube; no tumor cells in peritoneal washings or in ascites
IB	Tumor limited to both ovaries (capsule intact) or fallopian tubes, no tumor on the surface of ovary or fallopian tube; no tumor cells in peritoneal washings or in ascites
IC	Tumor limited to ovaries (one or two) or fallopian tube(s), with any of these:
IC1	Surgical spill
IC2	Tumor on the surface of ovary or fallopian tube or rupture of capsule prior to surgery
IC3	Tumor cells in peritoneal washings or in ascites
Stage II	Tumor involves ovaries (one or two) or fallopian tube(s) with a pelvic spread or primary peritoneal carcinoma
IIA	Spread to and/or implants on ovaries and/or fallopian tube(s) and/or the uterus
IIB	Spread to and/or implants on other pelvic tissues
Stage III	Tumor involves ovaries (one or two) or fallopian tube(s), or primary peritoneal carcinoma, with affirmed peritoneal metastasis outside the pelvis and/or retroperitoneal lymph node metastasis
IIIA1	Retroperitoneal lymph node metastasis only (microscopically affirmed)
IIIA1i	The biggest size of the metastasis up to and including 10 mm
IIIA1ii	The biggest size of the metastasis more than 10 mm
IIIA2	Microscopic extrapelvic peritoneal involvement with or without retroperitoneal lymph node metastasis
IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in the biggest size with or without retroperitoneal lymph node metastasis
IIIC	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in the biggest size with or without retroperitoneal lymph node metastasis (includes a tumor spread to the liver capsule or splenic capsule, but no spread to the parenchyma)
Stage IV	Metastasis to distant organs, such as pleural effusion containing tumor cells; metastasis to parenchyma of the liver or spleen; extra -abdominal metastasis (inguinal lymph nodes and lymph nodes outside the abdomen are also implied); involvement of intestinal wall
IVA	Pleural effusion containing tumor cells
IVB	Metastasis to parenchyma of the liver or spleen; extra -abdominal metastasis (inguinal lymph nodes and lymph nodes outside the abdomen are also implied); involvement of intestinal wall

Reference: Arora, Mullangi & Lekkala, 2021

2.8 Staging

The 8th edition American Joint Committee on Cancer (AJCC), International Federation of Gynecology and Obstetrics (FIGO)/Tumor, Node, Metastasis (TNM) staging system is used for the staging of EOC (Arora, Mullangi & Lekkala, 2021). Staging is displayed in Table 2.

2.9 Clinical management

The diagnosis EOC is made by histological examination and tissue for diagnosis is mostly provided by oophorectomy or salpingectomy or biopsies of the peritoneum. Once the diagnosis is made, the next step will be staging and cytoreduction.

Cytoreductive surgery is identified according to its timing and extent. "Primary cytoreduction" is surgery which is performed before chemotherapy. It is called "interval cytoreduction" when performed after neoadjuvant chemotherapy and "secondary cytoreduction" when performed after recurrence of the cancer. On the other hand, if no grossly visible tumor is left at the end of the surgery, it is named as "complete cytoreduction". According to the definition of the Gynecologic Oncology Group, the surgery is "optimal cytoreduction" when the maximum diameter of the residual tumor is ≤1 cm (Hoskins & ark., 1994), but it will be "suboptimal cytoreduction" if maximum tumor diameter is >1 cm.

Management of EOC patients typically includes adjuvant platinum- and taxane-based chemotherapy after surgical staging and cytoreduction. Optimal cytoreduction is believed to improve the probability of a long-term disease-free survival after chemotherapy. The residual tumor volume that is left after cytoreduction has inverse correlation with survival (Allen, Heintz & Touw, 1995). However,

neoadjuvant chemotherapy (NACT) is preferred to primary surgery in some cases, such as patients with a poor health status and the ones with advanced and unresectable disease in whom complete or optimal cytoreduction is not probably to be managed.

If no contraindications to primary cytoreduction have been detected, diagnostic laparoscopy can be effective for both surgical evaluation and to assess cytoreductive feasibility, especially in patients who have symptoms suggestive for EOC and/or ascites, with elevated tumor markers associated with EOC (Rutten & ark., 2017). Fagotti score, which is a laparoscopy-based quantitive scoring, can be used to assess the chance of optimal cytoreduction (Fagotti & ark., 2006). There are seven parameters in this scoring model as omental cake, diaphragmatic carcinomatosis, peritoneal carcinomatosis, metastasis to the liver, bowel and/or stomach infiltration and mesenteric retraction.

A midline vertical incision is mostly used for cytoreduction, but a minimally invasive technique may also be preferred in an appropriate, selected patient group. Standart staging method for EOC typically consists of total extrafascial hysterectomy and bilateral salpingo-oophorectomy including pelvic and paraaortic lymph node dissection (Heintz & ark., 2006). Cytology from ascites or pelvic wash samples, and omentectomy is performed. In the presence of bulky disease, debulking procedure may also include splenectomy, bowel resection, partial hepatectomy, and diaphragmatic resection.

An interval cytoreduction including hysterectomy and bilateral salpingo-oophorectomy with the resection of the residual

tumor may be performed for patients who have taken NACT, after three or four chemotherapy cycles.

Fertility preservation alternatives are limited for EOC patients due to diagnosis at advanced stage. It may only be preferred in patients who have borderline tunor or stage IA EOC and desire future childbearing.

The vast majority of EOC patients benefit from chemotherapy in the postoperative period. Therefore, most patients with early-stage cancer; especially the ones with high grade tumor, clear cell carcinoma or stage IC or II disease should undergo adjuvant chemotherapy. Similarly, advanced stage patients who have undergone surgical cytoreduction should also receive adjuvant chemotherapy. On the other hand, in patients with a poor health status and the ones with advanced and unresectable disease in whom complete or optimal cytoreduction is not probably to be managed; NACT may be preferred. Adjuvan therapy should be given as soon as feasable, especillay in 2-4 weeks after surgery.

Platinum-based chemotherapy is preferred in EOC, but treatment alternatives may change according to the spread of the tumor. Carboplatin and paclitaxel combination is the preferred regimen in early-stage patients. In advanced stage patients, treatment options differ according to whether optimal cytoreduction is managed or not. In patients whose surgery has ended with optimal cytoreduction; carboplatin (or cisplatin) and paclitaxel may be combined as intraperitoneal (IP) or intravenous (IV) options. Bevacizumab may be added to this regimen in some cases. However, in patients with suboptimally cytoreduced tumor, IP therapy is not an option. A platinum-based IV combination, like

carboplatin and paclitaxel is preferred instead. Maintenance therapy with poly (ADP-ribose) polymerase (PARP) inhibitors is suggested in cases with disease in remission after primary chemotherapy.

2.10 Prognosis

The prognosis of ovarian cancer is usually poor since it is usually diagnosed in advanced-stage. Relaps occurs in the vast majority of advanced-stage patients and as a result of this, mortality rates are high.

A study including 1900 stage III ovarian cancers has shown that the main prognostic features suggesting better outcome include younger age, residual disease with low volume, good health status and serous histology (Winter III & ark., 2007).

2.11 Posttreatment surveillance

Patients are usually monitored according to National Comprehensive Cancer Network (NCCN) guidelines (Armstrong & ark., 2022). The frequency of patient visits should be every 2-4 months for 2 years, then every 3-6 months for 3 years, then annually after five years. History, physical and pelvic examination should be included in visits. Follow-up for life is recommended for advanced stage patients who have achieved complete response. However, early-stage patients, who don't have any proof of recurrence at five years, can be directed to the primary care physician or gynecologist.

CA 125 or other markers are needed to be monitored at every visit if they were elevated at the time of diagnosis. Other laboratory and imaging studies should only be performed if there is indication, such as worsening symptoms or increase in CA 125 levels.

3. Non epitelyal over ca

95 percent of the ovarian malignancies are epithelial cancers; while the rest are germ cell tumors and sex cord-stromal tumors, derived from other types of ovarian cells (Robboy, 2009).

3.1 Ovarian germ cell tumors

Ovarian germ cell tumors (OGCTs) are derived from primordial germ cells of the ovary. They can be classified according to histologic subtypes as shown in Table 3.

Table 3: Classification of ovarian germ cell neoplasms

Teratoma Mature Immature Monodermal
Dysgerminomas
Yolk sac tumors
Mixed germ cell tumors
Rare subtypes Embryonal carcinomas Choriocarcinomas Polyembryomas

Reference: Serov, 1973

OGCTs account for about 20-25 percent of all ovarian tumors, whereas they form just 5 percent of malignant ovarian tumors (Tewari & ark., 2000). The age of patients mostly vary between 10-30 years and OGCTs form 70 percent of ovarian neoplasms diagnosed at this age group (Zalel & ark., 1996).

3.1.1 Clinical presentation

Patients may have no symptoms or they may have an abdominal mass, abdominal pain, precocious puberty, or abnormal uterine bleeding (Norris, Zirkin & Benson, 1976). Abdominal mass and pain are the most common symptoms and are seen in about 85 percent of the patients (Ueda & ark., 1990). OGCTs are usually large masses that grow rapidly, and rupture or torsion of the mass may cause abdominal pain. Precocious puberty and symptoms of pregnancy are suggested to occur due to HCG production of the tumor. In addition, spillage of the content of a mature teratoma into the abdomen as a result of rupture of the tumor may cause shock. Moreover, monodermal teratomas may cause hyperthyroidism or carcinoid symptoms.

3.1.2 Diagnostic evaluation

As always, the first step of diagnostic evaluation should include a complete medical history and physical examination. Pelvic ultrasonography is preferred as first-line imaging study in evaluating adnexall masses.

Laboratory studies include testing of certain tumor markers, since they are usually produced by OGCTs. Some tumor markers are mostly present in tumors of a specific histologic subtype (Mann & ark., 2000). These markers are used for assessment of the results of treatment and follow-up if they are elevated at the time of diagnosis.

Although the diagnosis may be strongly presumed before surgery due to the presence of an adnexal mass with elevated tumor markers, the definitive diagnosis is made by histology after the surgery.

3.1.3 Histopathology and pathogenesis

3.1.3.1 Teratomas

Mature Teratoma (Dermoid): They are mostly cystic and therefore they are also named as dermoid cysts. They contain elements differentiated from ectodermal (such as hair, skin or sebaceous glands), mesodermal (i.e muscle) and endodermal (eg, lung) tissues (Disaia, 1993).

Mature cystic teratomas form about 95 percent of ovarian teratomas and they are the mostly diagnosed ovarian tumors in women in their 20s and 30s (Ayhan & ark., 2000). They may also be detected in nonovarian sites (MacKinnon, Elmezzi & Phippen, 2021).

Macroscopically, a mature cystic teratoma is a cystic mass usually containing tooth, skin, hair in a thick sebaceous material. A solid protrusion called Rokitansky protuberance is seen between the normal ovarian tissue and the teratoma (Talerman & Path, 1987). Mature solid teratomas are mostly unilateral.

Patients with mature teratomas are usually asymptomatic. Torsion may commonly occur. Although it is rare, spillage of the content of a mature teratoma into the abdomen as a result of rupture of the tumor may lead to shock and hemorrhage. In the following period, a granulomatous reaction may cause dense adhesions.

Although mature teratomas are almost always benign (Ayhan & ark., 2000), malign transformation may occur in 0.2 to 2 percent of them (Singh & ark., 1988). The most common secondary neoplasm developing from a mature teratoma is squamous cell carcinoma that arises from the ectoderm (Hackethal & ark., 2008).

Immature Teratoma: They are also named as embryonal teratoma, teratoblastoma or malignant teratoma and they mostly occur in the first two decades (Disaia, 1993). Microscopically, they contain immature tissue usually with neural differentiation. The only histologically graded OGCTs are malignant teratomas and grade is associated with amound of the immature neural elements (Norris, Zirkin & Benson, 1976).

Monodermal highly specialized teratomas: They are rare teratomas that contain n evident histologic cell type. Struma ovarii and carcinoid neoplasms are the frequent tumors in this group. Struma ovarii consists of thyroid tissue (Disaia, 1993) and it may cause hyperthyroidism due to the secretion of thyroid hormones. Carcinoid neoplasms may cause symptoms such as flushing and diarrhea due to the secretion of bioactive polypeptides and amines. Carcinoid syndrome may occur and 5-hydroxyindoleacetic acid, which is a metabolite of serotonin and secreted in the urine, may be used as a marker to diagnose this syndrome.

3.1.3.2 Dysgerminoma

Dysgerminoma is the embryological counterpart of testicular seminoma. Dysgerminomas form about one-third of all ovarian malignant tumors in adolescents and young women (La Vecchia, Morris & Draper, 1983). Similarly, they are among the more common malignant tumors occuring in pregnancy.

Dysgerminomas often grow fast and cause abdominal enlargement and pain as a result of torsion or rupture. They can secrete placental alkaline phosphatase and lactate dehydrogenase (LDH) (Levato & ark., 1995), but they usually don’t produce alpha-fetoprotein (AFP). Bilaterality is much more common in

dysgerminoma than in other malignant OGCTs. Most dysgerminomas are detected at stage I disease (Gordon, Lipton & Woodruff, 1981).

Dysgerminomas vary from other malignant OGCT subtypes in many ways. They tend more to remain limited to ovaries at diagnosis, bilaterality is more common as mentioned before, they are more likely to spread predictably, and they are more sensitive to radiotherapy.

3.1.3.3 Yolk sac tumor (endodermal sinus tumor)

Yolk sac tumors account for 14-20 percent of malignant OGCTs (Smith & ark., 2006). They often arise in young females with a median age of 23 years and about one-third of the cases are premenarchal (Shah & ark., 2008). Microscopically, these tumors may contain Schiller-Duval bodies, which are invaginated papillary structures that have a central vessel (Talerman & Path, 1987). The growth of the tumor is usually rapid and aggressive. Alpha-fetoprotein (AFP) is strongly related with yolk sac tumors (Mann & ark., 2000).

3.1.3.4 Mixed germ cell tumors

They form about 5.3 percent of malignant germ cell tumors (Smith & ark., 2006). Two or more types of malignant germ cell tumors are contained in a mixed germ cell tumor. Yolk sac tumor mixed with dysgerminoma is the mostly diagnosed combination.

3.1.3.5 Embryonal carcinoma

Embryonal carcinomas form about 4 percent of malignant OGCTs (Smith & ark., 2006) and they are among the most aggressive ovarian malignant tumors. Diagnosis is usually made at a

mean age of 15 years. These tumors may secrete HCG and AFP (Disaia, 1993). Patients often present with abdominal pain and mass (Ueda & ark., 1990).

3.1.3.6 Choriocarcinoma

Choriocarcinomas are infrequent and very invasive tumors (Disaia, 1993). They are histologically identical to gestational choriocarcinoma (Wheeler & ark., 1990). All choriocarcinomas secrete HCG, which may lead to to irregular vaginal bleeding and isosexual precocity. HCG levels may be used for monitoring response to treatment. Ovarian choriocarcinomas have a tendency to develop early hematogenous metastasis to many organs. As opposed to gestational choriocarcinomas, ovarian choriocarcinomas are relatively unresponsive to chemotheraphy.

3.1.3.7 Polyembryoma

Polyembryoma is a very rare malignancy whose content is similar to normal embryos morphologically (Talerman & Path, 1987). Human placental lactogen (hPL), AFP and HCG may be elevated and pseudopuberty signs may occur as a result.

3.1.4 Staging and treatment

Surgery is preferred in almost all OGCTs not only for diagnosis, but also for staging and treatment. Removal of the cyst or ovary is performed and the sample is sent to frozen section at the beginning of the surgery. How the operation will continue is based on the results of the frozen section.

The vast majority of patients with OGCTs are diagnosed at stage IA disease, while 10-12 percent of the patients have bilateral tumors (Pectasides, Pectasides & Kassanos, 2008).

Mature cystic teratomas: Ovarian cystectomy is suggested for mature cystic teratomas, however, salpingo-oophorectomy may also be alternative for women who have completed childbearing. Benign cystic teratomas do not recur after resection.

Malignant OGCTs: International Federation of Gynecology and Obstetrics (FIGO) staging system for epithelial ovarian cancer is used for the staging of malignant OGCTs (Table 2) (Berek & Bast Jr, 2003), as identically in EOCs.

Surgical staging and optimal cytoreduction is performed by abdominal exploration in adults diagnosed with germ cell tumors. The staging method is identical to the one in EOC. Since the vast majority of OGCTs present at stage I, fertility-preserving surgery can be performed to such patients.

Since malignant germ cell tumors are very responsive to platinum-based chemotherapy, adjuvant chemotherapy is routinely given to most adults, with a few exceptions. Bleomycin, etoposide, and cisplatin (BEP) is the mostly preferred chemotherapy regimen.

3.1.5 Posttreatment surveillance

Most recurrences occur in two years after treatment. Therefore, post-treatment follow-up usually includes (Salani & ark., 2011) the evaluation of tumor markers (AFP, HCG), symptoms and physical examination more frequently for the first two years. Radiographic imaging studies are only performed in patients whose tumor markers were not elevated at the time of diagnosis.

Table 4: Classification of ovarian sex cord stromal tumors

Pure stromal tumors
Fibroma
Cellular fibroma
Thecoma
Luteinized thecoma associated with sclerosing peritonitis
Fibrosarcoma
Sclerosing stromal tumor
Signet-ring stromal tumor
Microcystic stromal tumor
Leydig cell tumor
Steroid cell tumor
Steroid cell tumor, malignant
Pure sex cord tumors
Adult granulosa cell tumor
Juvenile granulosa cell tumor
Sertoli cell tumor
Sex cord tumor with annular tubules
Mixed sex cord tumors
Sertoli-Leydig cell tumor
Well-differentiated
Moderately differentiated with heterologous elements
Poorly differentiated with heterologous elements
Retiform with heterologous elements
Sex cord-stromal tumors, not otherwise specified

Reference: Young, 2014

3.2 Sex cord stromal tumors

Ovarian sex cord-stromal tumors (SCSTs) (Table 4) are derived from stromal cells, the sex cord or both.

Benign SCSTs form less than 4 percent of benign ovarian tumors, while the malignant SCSTs form less than 8 percent of malign ovarian tumors. Patients with SCSTs are mostly diagnosed at early-stage disease (Quirk & Natarajan, 2005) and the prognosis usually good due to low grade and rare lymph node metastasis (Thrall & ark., 2011). The mean age at diagnosis is 50 years, while 12 percent of the patients are younger than 30 years (Quirk & Natarajan, 2005).

3.2.1 Clinical presentation

Patients usually present with an adnexal mass, while they sometimes have virilization or estrogen excess symptoms due to hormone secretion of the tumor (Busquets & ark., 2010). Virilization symptoms include hirsutism, acne, deepening voice, oligomenorrhea, clitoromegaly (Varras & ark., 2011). On the other hand, symptoms like precocious puberty, endometrial neoplasm or abnormal uterine bleeding are due to estrogen.

3.2.2 Diagnostic evaluation

Evaluation of patients suspected for SCSTs includes laboratory testing for androgens, estrogens and tumor markers, while imaging studies are also performed. Endometrial sampling should be done if abnormal bleeding or endometrial thickening is present.

All patients with an adnexal mass with features suggesting a malignant tumor should undergo surgery for resection and diagnosis.

3.2.3 Histopathology and pathogenesis

3.2.3.1 Pure stromal tumors

FIBROMA: These are the mostly diagnosed benign SCSTs. They are benign and they don't have an endocrine effect. About 10 percent of fibromas contain increased cellularity and mitotic activity (Prat & Scully, 1981). They are called cellular fibromas and are suggested to have low malignant potential.

THECOMA: They are rare, benign tumors that contain theca cells. They may also contain granulosa cells and will be named as granulosa-theca cell tumors then (Cronjé & ark., 1999).

LUTEINIZED THECOMA ASSOCIATED WITH SCLEROSING PERITONITIS: They are rare, benign tumors, but they may be related to considerable morbidity and sometimes mortality as a result of severe adhesions and bowel obstruction.

FIBROSARCOMA: They are very rare malignant tumors and their aggressiveness is associated with the degree of anaplasia and the number of mitoses.

3.2.3.2 Pure sex cord tumors

GRANULOSA CELL TUMORS: They account for 2-5 percent of malignant ovarian tumors and 90 percent of malignant SCSTs (Young, 2005). As a result, they are the mostly diagnosed malignant ovarian SCSTs. They have 2 subtypes; adult subtype accounts for 95 percent of the cases, while the juvenile subtype forms about 5 percent.

Patients usually present with an adnexal mass, resembling a mucinous cystadenoma and signs of excess estrogen. Rupture of the tumor or torsion may occur. Excess estrogen may lead to

endometrial hyperplasia or intraepithelial neoplasia in adults, while it may cause isosexual precocious puberty in prepubertal patients. Inhibin may be used as a tumor marker in these tumors.

SERTOLI CELL TUMORS: Sertoli cell tumors are infrequent. Excess estrogen symptoms may usually be seen, but virilization may also occur. Most cases are detected at stage I disease and are well differentiated, but they may also contain atypia and increased mitoses, resulting with a malignant behaviour (Young, 2005).

SEX CORD TUMORS WITH ANNULAR TUBULES: About 30 percent of these tumors are related to Peutz-Jeghers syndrome (PJS), which is an autosomal dominant disorder (Young & ark., 1982).

Almost all patients have symptoms due to elevated estrogen levels. PJS-associated SCTATs are generally benign, whereas 20 percent of sporadic SCTATs may be metastatic at the time og diagnosis (Young & ark., 1982).

3.2.3.3 Mixed sex cord-stromal tumors

SERTOLI-LEYDIG CELL TUMORS: They are rare tumors with four subtypes as shown in table 4. The retiform pattern includes projection which resemble the rete testis and rete ovarii. This pattern is related to increased serum levels of alpha-fetoprotein (Mooney, Nogales & Tavassoli, 1999). At least one-third of patients have virilization; but virilization is less common in retiform pattern (Ozdemir & ark., 2024). Sertoli-Leydig cell tumors are generally benign, whereas they may behave like malignant tumors when tumor grade is high.

3.2.4 Staging and treatment

Malignant SCSTs are surgically staged, either laparoscopically or with an open procedure. The staging system is the same as the one for all primary ovarian cancers. The stage is the most important prognostic factor (Miller & ark., 1997).

Complete surgical staging generally resembles the procedure in EOCs; however, there is a significant difference. Pelvic and paraaortic lymphadenectomy is not recommended in most SCST patients as lymph node metastasis is rare (Thrall & ark., 2011).

Total hysterectomy and bilateral salpingo-oophorectomy are performed during surgical staging, but fertility preservation may be possible in young patients with ovarian tumors confined to the ovary. Endometrial sampling is needed in patients who have an estrogen-secreting SCST, if hysterectomy is not performed.

Adjuvant therapy may be preferred, if needed, as a part of an individualized treatment strategy due to the lack of data for about it. The most common regimen for patients with SCSTs is bleomycin, cisplatin, etoposide (BEP).

3.2.5 Posttreatment surveillance

Post-treatment follow-up usually includes (Salani & ark., 2011) the evaluation of tumor markers (AFP, HCG), symptoms and physical examination more frequently for the first two years. Radiographic imaging studies are only performed in patients who have symptoms or elevation in tumor markers.

4.Conclusion

95 percent of the ovarian malignancies are epithelial cancers; and epithelial ovarian cancer is the main reason of gynecologic

cancer mortality, besides the fifth most important reason of woman cancer mortality in the United States. The main reason for the high mortality rates is that, patients are usually diagnosed at advanced stage disease due to the lack of specific symptoms. On the other hand, it has been proven that staging and cytoreduction by a gynecologic oncologist improves prognosis. Therefore, patients should be referred to a gynecologic oncologist if there is a high level of suspicion of cancer as a result of initial evaluation, which consists of physical examination, imaging by pelvic ultrasonography and laboratory studies of tumor serum biomarkers. Criteria for referral of a patient who presents with a pelvic mass have been identified by ACOG Guidelines. Contrary to the guidelines in 2002, there is no specific value for high CA 125 levels in the guidelines that are updated in 2011. The 8th edition American Joint Committee on Cancer (AJCC), International Federation of Gynecology and Obstetrics (FIGO)/Tumor, Node, Metastasis (TNM) staging system is used for the staging of ovarian cancers. Management of EOC patients typically includes adjuvant platinum- and taxane-based chemotherapy after surgical staging and cytoreduction. Optimal cytoreduction is the primary goal to achieve in surgery. Fertility preservation alternatives are limited for EOC patients due to diagnosis at advanced stage. It may only be preferred in patients who have borderline tunor or stage IA EOC and desire future childbearing.

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