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# Reproductive and Gynecologic Health Annual Volume 2025

*Edited by Courtney Marsh*





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### Aims and Scope of the Series

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Apart from being diverse, obstetrics and gynecology is a challenging and demanding specialty. It combines medical and surgical skills.

The sequence of books in this series will have certain characteristics in common that will be recognized as part of the same informative multi-volume book programme.



# Meet the Series Editor



Zouhair Amarin is a Professor of Obstetrics and Gynaecology at the Jordan University of Science and Technology. He was previously a lecturer at the University of Glasgow, Scotland, a senior lecturer at the University of Nottingham, England, and the dean of the Faculty of Medicine at Mutah University, Jordan. Professor Amarin is a fellow of the Royal College of Obstetricians and Gynaecologists, and the Faculty of Public Health, London. He holds master's degrees in medical science and medical education. He is a pioneer in IVF and was the first in the world to develop microsurgical epididymis sperm aspiration for clinical use. He also discovered a surgical procedure for critical ovarian hyperstimulation syndrome. Professor Amarin has edited books, authored book chapters, and published more than 130 papers. He is the recipient of eight awards.



# Meet the Topic Editor



Dr. Courtney Marsh is certified by the American Board of Obstetrics and Gynecology with a subcertification in reproductive endocrinology. She completed a fellowship at the University of Michigan. She earned her medical degree from the University of Kansas School of Medicine and completed her residency at Emory University. Dr. Marsh is passionate about helping couples get pregnant. She has published over fifty peer-reviewed journal articles and has authored multiple book chapters on reproductive physiology and infertility. Dr. Marsh has a busy clinical practice at the University of Kansas Health System, helping patients build families and manage complex reproductive hormonal issues.



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# Preface

This book explores the expansive topic of reproductive and gynecologic health, providing overviews of the most current practices and up-to-date research reviews. Reproductive health is a comprehensive examination of the well-being of the female reproductive system and its function over the lifespan. Phases include prepubescent, pubertal, reproductive, perimenopausal, and menopausal. Related to reproductive health is gynecologic health, which includes menstruation, contraception, and hormonal care to protect and promote the health of female reproductive organs.

This volume takes a deeper look at reproductive and menopausal phases of reproductive and gynecologic health. The first chapter, “Alteration of Fetal Growth”, looks at disorders related to the growth of the fetus in pregnancy with a focus on macrosomia and fetal growth restriction.

Next, we explore gynecologic cancers and advances in diagnoses and therapeutic options. The second chapter, “Role of Ultrasound in Cervical Cancer Assessment”, examines how a widely available diagnostic tool (ultrasonography) can be used in a novel way to characterize and diagnose cervical cancer. We then have three chapters dedicated to endometrial cancer. The third chapter of the book, “Diagnosis of Endometrial Carcinoma”, is a comprehensive review of the pathology and clinical skills needed to diagnose endometrial cancer, geared towards clinicians. The fourth chapter, “Endometrial Cancer – Prognostic Models and Risk Assessment”, further explores factors related to endometrial cancer and their effects on patient outcomes. Finally, the fifth chapter, “Long Noncoding RNAs in Endometrial Cancer: Prognostic Biomarkers, Molecular Mechanisms, and Therapeutic Potential”, reviews the latest research on endometrial cancer for both researchers and clinicians.

The last three chapters focus on hormone replacement and postmenopausal care of women. Chapter six, “Role of Nutrition in Menopausal Women”, explores the contemporary topic of the role of food and energy intake in managing postmenopausal changes. This chapter appeals to patients, clinicians, and ancillary health care providers seeking to optimize care after menopause. Chapter seven, “Postmenopausal Hormone Replacement Therapy for Health Maintenance during Aging”, provides a comprehensive review of exogenous sex steroid hormones in postmenopausal women and their effects on health and longevity. Finally, the last chapter, “Hormone Replacement Therapy: Is It Always Necessary in Natural and Surgical Menopause?”, looks at timing and dosing of hormones in women and the rationale for replacement.

Overall, this book provides a wide breadth of knowledge across multiple phases of reproductive and gynecologic health throughout a woman's life. Thank you for your interest, and enjoy!

**Courtney Marsh**  
University of Kansas School of Medicine,  
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Section 1

# Reproduction

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## Chapter 1

# Alteration of Fetal Growth

*Maria Fernanda Calderon Leon, Deborah Denisse Gaibor Santos, Diego Mauricio Cabrera Moyano, María Eugenia Ugarte Vega, Priscilla Eliana Robles Ordoñez, Mónica Piedad Moran Ayala, Gabriel Leon San Miguel, Jeaneth Paola Haro Fernández, Maritza Janneth Montesdeoca Samaniego and Javier Aquiles Hidalgo Acosta*

### Abstract

Fetal growth is a process that is not easy to assess and is regulated by multiple mechanisms that depend on many fetal, placental, and maternal factors. The birth weight percentile compared to the estimated gestational age reveals lower gestational ages for women and higher gestational ages for men in certain geographic areas such as Africa, with differences in comparison with the world population. The alteration in fetal growth is related to several perinatal complications such as intrauterine death, increased cesarean section, maternal-neonatal injuries, and shoulder dystocia. Among the main manifestations of fetal growth disturbance is intrauterine fetal growth restriction, which affects approximately 3–7% of all pregnancies and is defined as a condition in which the fetus fails to achieve the growth determined by its genetic makeup. Its diagnosis requires an estimated fetal weight by ultrasound lower than the 10th percentile for gestational age. The most outstanding maternal risk factor for fetal growth disturbance is maternal body mass index, where obesity predominates. Asymmetric or type II intrauterine growth restriction is more frequent in the second trimester of pregnancy.

**Keywords:** fetal growth retardation, fetal macrosomia, fetal weight, gestational age, fetal death

### 1. Introduction

This chapter is of great relevance due to the importance of an adequate perinatal assessment of fetal growth, through ultrasound and clinical parameters that determine alterations in the growth of the fetus.

Fetal growth is a physiological process influenced by multiple factors, it has two stages, the first is called the hyperplasia stage and lasts until the 20th week of gestation, then the hypertrophy and hyperplasia stage occurs, with an increase in fetal

size and goes from 20 to 28 weeks of gestation, from this last week, the stage of only hypertrophy occurs, with an increase in the size of the fetal organs [1].

Intrauterine growth restriction (IUGR) is one of the main manifestations of impaired fetal growth (IGF), which affects approximately 3–7% of all pregnancies and occurs when the fetus fails to achieve adequate growth (**Figure 1**). For its diagnosis, an estimated fetal weight by ultrasound (EFW) (**Figure 2**) lower than the 10th percentile for gestational age is required [2].

Its cause may be influenced by negative changes in fetoplacental-maternal nutrition, generating fetal malnutrition or also by limitations of intrauterine space that restrict fetal growth, causing significant complications.

IUGR can be symmetrical or asymmetrical. Symmetrical or type I, produced during the first trimester, due to a decrease in fetal nutrients, represents 20–30% of cases, and is associated with tobacco use, drugs, chronic hypertension, anemia, pre-existing diabetes mellitus, chromosomal abnormalities, infections by *Toxoplasma gondii*, cytomegalovirus, herpes simplex virus, varicella-zoster virus, treponema. It is called symmetrical restriction because all parameters are reduced proportionally [3].

Asymmetric IUGR or type II, occurs due to intrauterine aggression at the end of the second or third trimester of pregnancy, in a disproportionate manner, with preservation of the head circumference and reduction of the abdominal circumference with an ultrasound increase in the brain-liver ratio, whose main risk factor is preeclampsia [3].

The consequences of IUGR are serious and may include intrauterine death, premature birth, perinatal hypoxia, hypoglycemia, polycythemia, seizures, intracranial hemorrhages, and deficits in neurological and motor development, as well as multiple complications in adult life such as chronic arterial hypertension, stroke, and coronary heart disease.

It is important to recognize that a fetus may have a lower weight than expected because its growth potential is lower, therefore, it is growing correctly according to its predisposition and genetic factors; in these cases, the term “low weight for gestational age” is used and it is not a IUGR [4].



**Figure 1.**

*Description: there is evidence of altered fetal growth in a 26-week fetus, with fetal malformation (hydrops fetalis). The image shows a section of the abdominal circumference with ascites.*



**Figure 2.**

*Description: the image shows a 31-week fetal death with multiple malformations, delivered by cesarean section with difficult extraction due to large ascites.*

To estimate fetal growth, standard tables should be used that are related to ultrasound measurements in the second trimester of pregnancy. The tables or percentiles indicate how the fetus deviates, and the fetal measurement is based on the average value of the population [5].

When we refer to small for gestational age and large for gestational age, they are definitions of fetal size below or above a certain threshold related to a reference population and may be linked to an abnormal condition [4].

Physiologically, the placental regulation of fetal growth integrates multiple signaling pathways that modulate the functions of the placenta, including nutrient transport. When the supply of oxygen and nutrients to the fetus is altered, changes in placental and fetal growth are caused. For example, when placental insulin/insulin-like growth factor-1 and cell signaling pathways and amino acid transport are inhibited, IUGR occurs, and conversely, when it is activated, macrosomia is generated [6].

Other factors influence fetal development: vitamin D levels. Deficiency of this vitamin is associated with adverse anthropometric outcomes in offspring and adverse neurological outcomes [7].

The etiology of fetal macrosomia, due to maternal causes, is related to diabetes in pregnancy and maternal obesity; the latter is related to an increase of 4 to 12 times of fetal macrosomia, whose metabolic basis is the increase in insulin resistance and hyperinsulinemia, however, other fetal causes are also found such as fetal gender, since it is observed more in the male gender than in the female. Genetic and

congenital disorders, such as Beckwith-Weiderman syndrome, Sotos syndrome, Fragile X syndrome, Weaver syndrome [8].

Women who have had previous macrosomic babies have a five to ten times higher risk of having another macrosomic baby [7].

The objective of this research is to describe fetal growth disorder.

## **2. Methodology**

Articles on the research topic published with available results were selected by inclusion and exclusion. Inclusion criteria were articles on fetal growth disorders, risk factors associated with fetal growth disorders, ultrasound diagnosis of perinatal development with fetal disorders. Inconclusive articles and articles without results that did not address the research topic were excluded. The articles were obtained from databases such as the National Library of Medicine, Pubmed, Elsevier, and journals such as *Nature*, *BMJ*, *JAMA*, and the *New England Journal of Medicine*. The last search date was February 5, 2025.

## **3. Discussion**

In a study conducted in the second trimester of pregnancy in 70 women with isolated hypothyroxinemia, there were no significant differences in perinatal complications in the first and second trimester of pregnancy [9], while isolated maternal hypothyroxinemia in the third trimester of pregnancy is associated with poor outcomes [8].

Fetal overgrowth is related to several perinatal complications such as fetal death, increased cesarean section, maternal-neonatal injuries, and shoulder dystocia [10].

According to the American Pregnancy Association, intrauterine growth restriction (IUGR) is defined as a fetal weight below the 10th percentile for gestational age determined by ultrasound [11–13].

Assessment of fetal growth by ultrasound reduced fetal morbidity with better neurological outcomes in the planned delivery group [14].

Excessive gestational weight gain alters DNA methylation and influences fetal and neonatal body composition [9].

The biparietal diameter has shown the ability to determine large for gestational age, adequate for gestational age birth, but is more effective from the third trimester onwards [15].

Nutrition during pregnancy plays an important role in influencing fetal and maternal outcomes since the intake of vegetables, fruits, whole grains, and fiber may represent lower levels than recommended; however, currently, with the obesity epidemic, the relative proportion of sodium, fats, and carbohydrates appears high, influencing weight gain during pregnancy, development of gestational diabetes and fetal growth restriction, also affecting maternal nutritional status after pregnancy [16].

Maternal obesity, diabetes, and many genetic disorders can affect fetal growth and development because the supply of nutrients to the fetus depends on placental transport and if there are metabolic alterations there will be a nutritional imbalance for the fetus, whose requirements are determined by the growth rate, the composition of new tissues and the metabolic rate [16].

Adequate intake of calories, protein, minerals, vitamins and long-chain fatty acids is important for brain function and offspring behavior in humans. Fetal malnutrition causes growth retardation and has detrimental effects on the development and subsequent functioning of fetal organs [17].

Maternal obesity increases the risk of developing perinatal complications and cesarean delivery with long-term implications in the development of metabolic and cardiovascular diseases in the future. Sleep problems also have an influence, affecting adequate fetal growth and development; therefore, nutrition and metabolic factors during the first years of life play a key role in health promotion and nutrition programs for public health worldwide [17].

In relation to this, early programming is mentioned, which is defined as the adaptation process by which nutrition and other environmental factors alter fetal development in the uterus, thus inducing changes in metabolism and susceptibility to chronic diseases in adulthood. It is important to note that some studies carried out on animals have shown that the fetus can adapt to malnutrition by altering its hormonal production or the sensitivity of tissues to hormones, and insulin plays a key role in regulating fetal growth and therefore the need for nutrients [17].

The fetus can alter its metabolism, for example, by changing the oxidation of glucose to that of amino acids. It can also redistribute blood flow to major organs such as the brain and can even adapt to slower growth to decrease substrate demands, but unlike adults these changes in the fetus are permanent and definitive in its body structure and function. Thus, the fetal period has great plasticity and capacity to respond to maternal lifestyle and environment with induction of permanent DNA methylation [17].

It is worth highlighting other environmental factors and maternal habits such as fetal exposure to alcohol that can cause many developmental disorders, such as deterioration of fetal growth and the development of multiple organic systems, producing what is known as fetal alcohol spectrum disorders, which occurs as a consequence of alcohol-induced malabsorption, with alteration of the intrauterine environment generating fetal development deficits and harmful effects in relation to nutrient homeostasis with teratogenic effects [18].

The most severe form of fetal alcohol spectrum disorder is called fetal alcohol syndrome. The negative effect of alcohol during pregnancy is not only environmental but also directly affects the molecules and pathways that control fundamental processes of fetal development, and it is important to note that nutritional deficiencies can worsen the teratogenic effect of alcohol [18].

Nutrients pass to the fetus through specific transporters present in the microvilli and basement membrane of the placenta, because all mammalian species depend on the placenta, a transitory organ, for the exchange of gases, nutrients and wastes between the mother and the fetus [19].

Glucose is the most abundant nutrient transmitted to the fetus, playing an important role in its growth and development. Maternal glucose concentration influences the expression and activity of GLUT in the microvilli for glucose uptake and the basement membrane for glucose delivery, and it is necessary to recognize that alterations in the function or quantity of these transporters can affect the growth and body composition of the fetus [19].

The placenta, in addition to serving as a conduit for nutrient exchange, produces hormones and other factors that influence maternal physiology and fetal development, as well as neurotransmitters, such as serotonin, dopamine, norepinephrine/epinephrine, which can circulate and influence brain development. Neurobehavioral

disorders, such as autism spectrum disorders, probably have their origin in placental pathophysiological effects [20].

Birth weight is used to assess perinatal outcomes of fetal growth. Babies who are born too large for their age or too small may have an altered delivery pattern, whether cesarean or vaginal, as well as facing other long-term disorders, such as metabolic diseases and neurodevelopmental delay [21].

When dealing with twin pregnancies, fetal growth patterns may vary from 26 weeks of gestation and continue to increase until delivery; therefore, careful monitoring is necessary from 26 weeks of gestation for those women who have small fetuses for gestational age [21].

The thyroid gland also plays an important role in fetal growth because its function in metabolism is crucial, regulating body heat, energy levels, weight, hair, nails and menstrual cycles. There are physiological or pathological phenomena that can influence the functioning of the thyroid. Pregnancy is a physiological factor. There are many physiological and psychological changes that occur during pregnancy. An alteration of the thyroid in the mother is an example. Thyroid irregularities are the result of a lack of adaptation to new circumstances. Thyroid hormone levels may decrease, or production may slow down during pregnancy due to variations in the concentration of the hormone, producing gestational hypothyroidism or it may be present before pregnancy. The importance of mentioning the thyroid in this chapter lies in determining the effects that can occur in the fetus when the maternal thyroid gland is affected, for example cretinism and mental disorders are among the serious health problems related to an iodine imbalance in maternal hypothyroidism. The growth of the brain, nervous system and intelligence of a fetus depend on thyroid hormones [22].

A meta-analysis aimed to investigate the impact of maternal diabetes on fetal epicardial fat thickness measured by ultrasound and concluded that maternal diabetes during pregnancy is associated with increased fetal epicardial fat [23].

In a review that aimed to investigate the clinical implications of using the myocardial performance index (MPI), obtained by tissue Doppler imaging (TDI) and spectral Doppler, to assess fetal cardiac function in growth-restricted fetuses, they found that as conventional Doppler parameters deteriorate, myocardial performance index values increase, suggesting progressive myocardial dysfunction [24].

They observed elevated MPI levels in both growth-restricted and small for gestational age fetuses, indicating prenatal cardiac impairment [24].

There is a strong association between abnormal MPI and perinatal mortality, mainly in fetuses with early growth restriction [24].

In a Household Air Pollution Intervention Network (HAPIN) randomized controlled trial conducted in ten resource-limited settings in Guatemala, India, Peru, and Rwanda, pregnant women aged 18–34 years, 9–19 weeks pregnant, were randomly assigned 1:1 to receive a continuous LPG fueled cookstove or to continue regular biomass cooking for 18 months [25].

They performed ultrasound assessments at baseline, at 24–28 weeks' gestation (the first pregnancy visit), and at 32–36 weeks' gestation (the second pregnancy visit) to measure fetal size; they monitored personal exposures to 24 ha of home air pollutants during these visits; and they weighed the infants at birth [25].

They performed analyses to estimate differences in fetal size between the intervention and control groups, and exposure-response analyses to identify associations between home air pollutants and fetal size. They found no differences in mean

post-randomization Z scores for head circumference (0.30 vs. 0.39;  $p = 0.04$ ), waist circumference (0.38 vs. 0.39;  $p = 0.99$ ), femur length (0.44 vs. 0.45;  $p = 0.73$ ), or estimated or birth weight ( $-0.13$  vs.  $-0.12$ ;  $p = 0.70$ ) between the intervention and control groups. Personal exposure to home air pollutants was not associated with fetal size [25].

Another study aimed to evaluate the most recent evidence on clinical outcomes and safety of PDE-5 inhibitors for the management of FGR and concluded that sildenafil increased birth weight, prolongation of pregnancy, and umbilical artery pulsatility indices, but also increased the risk of pulmonary hypertension in newborns, as well as headache and hot flashes/rash in mothers, so further studies on this research topic are required [26].

#### **4. Conclusion**

The alteration of fetal growth is influenced by multiple maternal and environmental risk factors that influence its development, such as the presentation of preeclampsia, generating intrauterine growth restriction or metabolic disorders such as diabetes mellitus and obesity that generate alteration of macrosomia in the fetus, impacting on complications in childhood and adulthood with cardiovascular and cerebrovascular problems due to an alteration in fetal development; therefore, it is important to detect these anomalies by strict ultrasound control, mainly from the second trimester of gestation with growth percentile control.

Adequate nutrition and a supportive intrauterine environment are essential for healthy fetal development, and it is equally important to identify the contribution of the mother's nutritional status before and during pregnancy, in addition to alcohol-induced gestational side effects.

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#### **Conflict of interest**

The authors declare no conflict of interest.

#### **Acronyms and Abbreviations**

|      |                                      |
|------|--------------------------------------|
| DNA  | acid desoxyribonucleic               |
| IUGR | intrauterine growth restriction      |
| EFW  | estimated fetal weight by ultrasound |

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## Section 2

# Carcinoma

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# Role of Ultrasound in Cervical Cancer Assessment

*Almaz Gadisa Gurmu and Zegeye Wubeshet Haile*

### Abstract

Cervical cancer is a common gynecological cancer worldwide. The use of imaging modalities for pre-treatment workups for cervical cancer is growing. Ultrasound is less expensive, faster, and more generally available than other imaging modalities for the evaluation of cervical cancer. It is also a portable imaging radiological imaging modality. The clinical application of ultrasonography in cervical cancer has been improved by sophisticated ultrasonography techniques. Ultrasound provides very precise information on the presence of tumors and the extent of localized tumors. It is also important for precise preoperative staging and assessing treatment response. In this chapter, the role of ultrasound in assessing cervical cancer will be discussed.

**Keywords:** cervical cancer, ultrasound, staging, screening, response prediction

### 1. Introduction

Cervical cancer is a frequent gynecologic malignancy in women. In terms of both incidence and death, it ranks fourth in global cancer statistics for 2018. About 90% of the 342,000 cervical cancer-related deaths took place in low- and middle-income nations. South-East Asia, Central America, and Sub-Saharan Africa (SSA) have the greatest incidence and fatality rates of cervical cancer [1]. The updated 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system includes imaging and pathology assessments for cervical cancer [2].

Cervical cancer pre-treatment work-up is using more and more imaging modalities [3]. To create treatment plans, imaging modalities like positron emission tomography (PET), computed tomography (CT), and magnetic resonance imaging (MRI) were used. However, these services are expensive, not readily available everywhere, especially in low-income nations, necessitate the administration of intravenous contrast media, take a long time to scan, and are not real time [4].

Nonetheless, in recent years, ultrasonography has gained popularity as an imaging method for examining women with cervical cancer [5]. In comparison to other imaging techniques for the evaluation of cervical cancer, ultrasound is faster, radiation-free, less expensive, non-invasive, does not need a contrast agent, and is more readily available [6]. Furthermore, modern ultrasound technology has advanced in recent decades, and image quality has improved. High-frequency transvaginal

and transrectal ultrasound, when the probe is placed close to the tumor, can produce detailed images of the cervical tumor [6]. This chapter attempted to present the role of ultrasound in cervical cancer assessment.

## **2. Cervical cancer screening with ultrasound**

Using three-dimensional (3D) power Doppler ultrasound indices, the characteristics of cervix blood flow in normal women and women with precancerous lesions or invasive cancers were reported, comprising blood flow and vascularization as well as the number of vessels in the volume of interest and the flow intensity at the time of volume acquisition [7]. Enhancing ultrasound-based cervical cancer screening could be important, especially for women who are fertile. This would help reduce the unnecessary use of cervical biopsy or conization treatments [4].

## **3. Cervical cancer: local staging**

A comprehensive evaluation to determine the extent of cervical cancer should be performed if the diagnosis has been identified. Several investigations were conducted to detect the spread of cervical cancer lesions.

### **3.1 Transvaginal/transrectal ultrasound for local staging of cervical cancer**

The use of ultrasound for cervical cancer staging was first described in the early 1990s [8].

Transrectal ultrasound (TRUS) reliability for cervical cancer staging was previously documented [9]. Innocenti et al. compared clinical staging to transrectal ultrasonography in a group of 124 women diagnosed with cervical cancer. TRUS was found to be more sensitive (78%) than clinical exams (50%) for detecting parametrial infiltration. The sensitivity, specificity, and accuracy of TRUS for the extent of parametrial involvement were 78%, 89%, and 87%, respectively [9].

TRUS and MRI were compared in early-stage cervical carcinoma by Fischerova et al. [10]. In a group of 95 cases, they found that TRU was more sensitive than MRI for detecting parametrial involvement (83% vs. 50%) and was able to more clearly detect tiny cervical tumors (1 cm) [11].

In a study employing histology as the gold standard, Gaurilcik et al. evaluated TVS's capacity to define the location and quantify the size of early cervical cancer [12]. There was a strong connection.

The outcomes of a recent European multicenter trial comparing TVS and MRI for defining cervical malignancy were published by Epstein et al. These findings demonstrated that TVS was superior to MRI in both women who underwent a cone biopsy prior to surgery and those who did not [13].

A prospective study [14] focused on the diagnostic abilities of TVUS and MRI for determining the presence and extent of cervical cancer. Those with locally advanced cervical cancer scheduled surgery following neoadjuvant therapy, while those with early-stage cervical cancer planned for main surgery. The presence of the tumor was detected by TVUS or MRI in 56/60 (93%) and 53/60 (88%) patients, respectively. With regard to the parameters examined, such as the detection of the depth of stromal invasion to be greater than two-thirds, both ultrasonography and MRI exhibited

equivalent sensitivity and specificity. The inexpensive cost and ubiquitous availability of ultrasound make it superior to MRI [14].

### **3.2 Three-dimensional ultrasound (3DUS) scan**

The size of the tumor plays a key role in determining a patient's prognosis for cervical cancer. A 3D ultrasound system was reported to have computed the true volume of cervical cancer more precisely than a 2D ultrasound system [15].

The study, which involved 14 cervical cancer patients who got transvaginal volume ultrasound examinations before surgery, showed that three-dimensional multiplanar sonography is a promising method for the local staging of cervical cancer. The results of 3D ultrasonography were consistent with pathology in 12 of the 14 instances [16].

In a series of 24 women with cervical cancer, Byun et al. compared 3DUS, MRI, clinical exam, and surgical staging [17]. According to their findings, 3DUS had a higher accuracy rate (67%) than the pelvic exam (62%) and MRI (41%).

In a recent study, local staging of cervical cancer was reported for 46 patients who had pelvic MRIs and high-resolution transvaginal ultrasound (TVUS) scans [18]. The analysis of the tumor volume in both early-stage and late cervical cancers revealed a significant association between TVUS and MRI. A useful and affordable imaging technique for local cervical cancer staging is ultrasound [18].

The stage of invasive cervical cancer was determined by three-dimensional transvaginal ultrasonography (3D-TVUS), which was then compared to MRI for locally advanced cervical cancer [17]. TVUS had a sensitivity of 75%, MRI had a sensitivity of 75%, and clinical examination had a sensitivity of 25%. TVUS had a specificity of 90%, MRI had a specificity of 55.6%, and TVUS had an accuracy of 87.5%. According to the authors, preoperative 3D-TVUS may prove to be a very effective method for evaluating cervical cancer that has already spread locally [17].

## **4. Ultrasound findings as prognostic factors**

Angiogenesis has been demonstrated to be an independent prognostic factor and to predict recurrence in cervical cancer [19, 20]. Using transvaginal Doppler ultrasound, tumor angiogenesis can be evaluated in vivo and non-invasively [21].

### **4.1 Transvaginal color doppler in cervical cancer**

Transvaginal Color Doppler in cervical cancer allows non-invasive assessment of tumor angiogenesis.

Hsieh et al. published a paper in 1995 [22] that examined the intratumoral arteries in cervical cancer. Transvaginal color Doppler sonography was used by these authors to determine that 46.2% of cervical tumors showed blood flow color signals. When compared to individuals with no discernible color signals, they found that lymph node involvement was more common in those with detectable color signals (33% vs. 5.7%), and this was similarly correlated with a higher cell proliferation index.

For the in vivo evaluation of angiogenesis in patients with cervical cancer, Cheng et al. reported the development of a novel vascular index (VI) [23]. They used transvaginal power Doppler ultrasound to assess 35 patients with stage Ib-IIa cervical cancer, and they used image processing software to create a vascular index for each tumor. It was found that the probability of pelvic lymph node metastases increased

with a higher vascular index, deeper stromal invasion, and a higher incidence of lymphovascular space invasion. In order to evaluate intratumoral vascularization in 35 women with cervical cancer and 30 healthy women, Wu et al. compared color and power Doppler [24]. They discovered that color signals were present in 97% of malignancies and that patients with cervical cancer had considerably lower levels of both PI and a vascular ratio (defined as the cross-sectional area of intratumoral arteries divided by the cross-sectional area of the tumor). Given that the vascular ratio provided more sonographic features among the various sub-classifications of cervical cancer, they came to the conclusion that power Doppler angiography was more beneficial than color Doppler.

According to Alcazar et al., tumor blood flow as measured by transvaginal color Doppler was linked with some tumor features in 100% of cases of cervical cancer. Squamous cell malignancies, moderately or poorly differentiated lesions, and advanced-stage tumors all had increased levels of tumor vascularization [25].

With contentious findings, some investigations assessed the function of the three-dimensional power Doppler in cervical cancer. In a group of 74 cervical cancers, Testa et al. [26] found no association between 3D-derived vascular indices and clinic-pathological characteristics. However, 141 women with early-stage cervical cancer were studied using 3D Power Doppler, and Hsu et al. have presented their findings. They found blood flow in 85% of the tumors and discovered a correlation between tumor volume and tumor vascularization [27]. On the other hand, Alcazar et al. [28], Tanaka and Umesaki [29], and Belitsos et al. [7] found a correlation between specific tumor features, such as tumor stage and histologic grade, and tumor vascularization as determined by 3D power ultrasound.

## **5. Ultrasound for therapy response prediction**

Several studies have been conducted to assess the role of ultrasound in predicting treatment response in women with cervical cancer.

### **5.1 Prediction of neoadjuvant chemotherapy response**

Utilizing 3D Power Doppler Ultrasound, researchers examined the usefulness of transvaginal ultrasound in the early prediction of the pathological response in a large series of patients with locally advanced cervical cancer who underwent major surgery followed by neoadjuvant chemotherapy. The study included 88 of the 108 patients. Patients with a partial response showed significantly larger tumor volumes after 2 weeks of neoadjuvant treatment than those with a complete response. The partial response group had a lower vascularization index (VI) before and after 2 weeks of treatment than the complete response group [30].

The use of the Power Doppler vascularity index (PDVI) to predict response to neoadjuvant chemotherapy (NACT) in bulky early-stage cervical cancer was described. A transvaginal power Doppler was used to evaluate the response to NACT in 25 women with bulky early-stage cervical carcinoma treated with NACT followed by surgery. Twelve (48%) individuals responded to NACT, while thirteen (52%) remained stable or had worsening disease after NACT [31].

42 cervical cancer patients who were referred for NACT and had locally progressing disease participated in a prospective trial. Women with locally advanced cervical cancer had TRUS and MRIs to determine the size of their tumors after neoadjuvant

treatment. For patients with cervical cancer undergoing neoadjuvant chemotherapy (NACT), TRUS may be a reliable diagnostic tool for assessing tumor volume [32].

## **5.2 Response to neoadjuvant chemotherapy and radiation prediction**

Using 2D ultrasound parameters, 3D power Doppler, or contrast-enhanced indices, patients with locally advanced cervical cancer who underwent radical surgery after chemoradiation were assessed for the remaining tumor [33]. The results showed that in patients with locally advanced cervical cancer, grayscale and color Doppler ultrasonography perform poorly as a diagnostic tool for identifying disease that persists following neoadjuvant chemotherapy and radiation [33].

Two investigations were carried out by Alcazar et al. [34, 35] to evaluate the function of transvaginal color Doppler in predicting the clinical and pathological response to chemoradiotherapy in cases of locally advanced cervical cancer. They discovered that malignancies with fewer blood vessels responded more favorably than those with more.

## **5.3 Radiotherapy response prediction**

Grayscale and color Doppler ultrasonography were used to assess the treatment response in cervical cancer patients [36]. Thirteen patients with advanced stages of cervical cancer were included in this study. Six months prior to and six months following radiation therapy, the patients underwent transvaginal color Doppler ultrasound and MRI exams. A complete response to treatment was significantly correlated with greater resistance indices. There was a substantial association between the MRI findings and resistive indices. The characteristics obtained with transvaginal color Doppler ultrasonography could be a useful alternative to MRI in evaluating the response of cervical cancer to treatment [36].

## **5.4 Response to concurrent chemoradiation**

Transvaginal color Doppler sonography has been shown to be beneficial in predicting clinical response to concomitant chemoradiation for locally advanced cervical cancer [35]. There were 21 individuals with locally advanced cervical cancer in the study. Before starting concurrent chemoradiotherapy, the patients had their tumor vascularity assessed with TVCD. The metrics included the lowest pulsatility index (PI), lowest resistance index (RI), and highest peak systolic velocity (PSV) from intratumor central vessels [35]. Complete clinical response (CR) was achieved in 11 patients (52%), while partial clinical response (PR) was reached in 10 patients (48%). PI was higher in CR tumors than in PR cancers; RI was higher in CR tumors than in PR tumors. In PSV, no differences were discovered.

## **5.5 Ultrasound in intraoperative guidance**

A recent retrospective study explored the role of intraoperative ultrasonography guidance in intracavitary brachytherapy for cervical cancer. Ultrasound guidance was used for tandem selection and proper application. Intracavitary brachytherapy was performed under ultrasound guidance for 412 insertions in 113 cervical cancer patients. One of the 113 patients treated with ultrasound guidance had uterine perforation, one had tandem myometrium, and one had a short tandem length. Intraoperative sonographic guidance improved the efficiency of intracavitary

brachytherapy for cervical cancer and reduced perforation rates [37]. The earlier study, which involved intraoperative ultrasonography guidance during intracavitary brachytherapy applicator placement for cervical cancer patients, yielded similar outcomes [38]. Intraoperative ultrasonography guidance enhanced the success rate of applicator placement [38].

## **6. Conclusion**

Accurately identifying the extent of the tumor and choosing the best course of therapy for patients with cervical cancer depend on the imaging performed during the basic diagnostic work-up. In cervical cancer, sonography could be a valuable technique for assessing the local extent of the illness. This approach is only useful for determining the status of lymph nodes. Doppler ultrasonography tumor vascularization could be used to monitor and predict response to therapy. Including ultrasound examination in cervical cancer screening, staging, and predicting therapy response plays a significant role, particularly in low-income countries where advanced imaging modalities are not available.

## **Conflict of interest**

The authors have declared that no competing interest exists.

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Section 3

# Carcinoma – Endometrial Cancer

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# Diagnosis of Endometrial Carcinoma

*Nighat Hussain, Renuka Gahine, Jayanti Chandrakar,  
Sakshi Jain and Roshan Hussain*

## Abstract

Endometrial carcinoma (EC) is the most common invasive malignancy of the female genital tract and a major global health concern, with increasing incidence and mortality driven by obesity, metabolic syndrome, and aging populations. This chapter provides a comprehensive overview of the diagnostic and molecular landscape of EC, highlighting the transition from conventional histopathological evaluation to integrated molecular classification. It discusses the clinical presentation, diagnostic pathways, histologic and immunohistochemical markers, and recent updates from The Cancer Genome Atlas (TCGA) defining four major molecular subtypes—POLE-ultramutated, MMR-deficient, p53-abnormal, and NSMP. The integration of molecular testing (POLE, MMR, and p53) into routine practice refines prognostication and guides precision therapy, including immunotherapy and targeted agents. Emphasis is placed on risk-adapted management, fertility-sparing options, and addressing global disparities in access to diagnostics and novel treatments. Future directions include AI-driven diagnostics, cost-effective molecular testing, and equitable implementation of personalized care in low-resource settings.

**Keywords:** endometrial carcinoma, molecular classification, POLE mutation, p53, mismatch repair deficiency

## 1. Introduction

Endometrial carcinoma (EC), arising from the epithelial lining of the uterus, is the most common invasive malignancy of the female genital tract in the developed countries [1]. Endometrial cancer remains the fourth most common cancer among US women [2]. The latest US data for 2025 show approximately 69,120 new cases and 13,860 deaths due to uterine cancer, an alarming and rising public health concern [3]. In less than a decade, new cases have increased by over 25%, and annual deaths have risen by more than 35%. The rising trend is particularly evident among younger women and women of color, especially Black, Hispanic, American Indian, and Pacific Islander [4].

In the United Kingdom, an estimated 8000 to 10,000 new cases are reported annually. Globally too, the burden of EC continues to rise, primarily due to increasing rates of obesity, metabolic syndrome, and aging populations- risk factors that not only increase incidence but also complicate treatment and survivorship [5, 6].

The lifetime risk of developing EC is estimated at 2.6–3% [7]. Although early-stage EC generally has a favorable prognosis, mortality rates have remained relatively stable over the past decades [5]. This paradox is driven by the limitations of traditional histopathological classification systems, which fail to capture the underlying biological and clinical heterogeneity of the disease. Consequently, patients with aggressive molecular subtypes may be undertreated, while those with low-risk disease may be exposed to unnecessary interventions [8].

Management of advanced or recurrent disease remains especially challenging due to limited therapeutic options and treatment resistance. Furthermore, inequities in access to timely diagnosis, molecular testing, and novel therapies persist across socioeconomic and racial lines. Fertility-preserving strategies are underutilized in young women, and the implementation of molecular diagnostics into routine care is still inconsistent, hindered by cost, infrastructure, and interpretive complexity.

This chapter presents a comprehensive and up-to-date overview of EC, highlighting both traditional diagnostic approaches and recent molecular advancements. It explores diagnostic pathways, prognostic markers, and therapeutic options—including surgery, radiation, systemic therapies, immunotherapy, and targeted agents. With a focus on risk-adapted, patient-centered care, it aims to support the clinicians in integrating emerging evidence into practice and addressing ongoing gaps in outcomes and equity.

## 2. Diagnosis of EC

The diagnostic process for endometrial carcinoma begins with the receipt of a well-filled requisition form containing relevant and detailed clinical information. The pathologist plays a central role in this process, and the biopsy must be interpreted in the appropriate clinical context.

### 2.1 Clinical information on histopathology requisition form

The essential clinical information that should accompany the specimen being sent to histopathology includes [9]:

#### 2.1.1 Patient's age, menopausal status, presenting symptoms, and risk factors

EC is often diagnosed at an early stage due to early-onset symptoms [10], especially in post-menopausal (PM) women. The most common presenting symptom is:

- Abnormal uterine bleeding—Occurs in >90% of cases, particularly postmenopausal bleeding (PMB) [7]
  - In premenopausal women, EC may present as irregular, heavy, or intermenstrual bleeding

Other, less common symptoms include:

- Pelvic or lower abdominal pain,
- Vaginal discharge (especially in advanced cases),
- Weight loss, fatigue (in advanced or metastatic disease).

Any PMB warrants prompt evaluation due to the high risk of malignancy.

EC is primarily driven by prolonged estrogen exposure unopposed by progesterone, often in the context of hormonal and metabolic imbalances. Up to 50% of cases are linked to obesity and estrogen-related pathways [11].

Hormonal and reproductive factors are as follows [12]:

- Unopposed estrogen exposure (e.g., estrogen-only HRT, estrogen-secreting tumors),
- Early menarche and late menopause,
- Nulliparity, infertility, and delayed childbirth,
- Tamoxifen use.

Metabolic and endocrine factors are as follows [12]:

- Obesity: 54% increased risk per 5-unit BMI increase,
- Diabetes and glucose intolerance,
- Polycystic ovary syndrome (PCOS): Nearly 3× increased risk,
- Hypertension and metabolic syndrome.

Protective factors include [13]:

- Progesterone exposure (e.g., through combined HRT or oral contraceptives),
- Pregnancy and parity,
- Oral contraceptive use: 26–43% reduced risk,
- Oophorectomy: Strongly protective,
- Physical activity,
- Caffeine (especially coffee): Modest risk reduction,
- Smoking: Modestly protective due to anti-estrogenic effect (not recommended as a preventive strategy).

Family history of Lynch syndrome (LS) or hereditary cancers: LS constitutes 3–5% of EC cases and is caused by germline Mismatch repair (MMR) gene mutations and confers a 40–60% lifetime risk of EC and colon, with EC often presenting first. Cowden syndrome (PTEN mutations) carries a 20–30% risk of EC [14].

### *2.1.2 Imaging*

*First-line investigations include the following:*

- Transvaginal ultrasound (TVUS) [15]
  - First imaging modality for women with PMB,
  - Endometrial thickness > 4 mm in a PM woman warrants further evaluation with endometrial sampling,
  - Useful for assessing uterine size, myometrial invasion, and other pelvic pathology.

*For staging and surgical planning*

Although EC is primarily a surgically staged disease, imaging is crucial for preoperative planning (**Table 1**).

*2.1.3 Type of specimen submitted*

*Endometrial sampling includes [16]:*

Histologic confirmation is required for diagnosis. The methods include are mentioned in **Table 2**.

In cases with persistently abnormal bleeding and normal biopsy, hysteroscopy is recommended to rule out focal pathology such as polyps or localized carcinoma.

The samples should be sent to the histopathology laboratory in neutral-buffered formalin in ratio of 1:20. Molecular testing is done preferably on curettings or biopsy as it is expected to be better fixed.

| Imaging modality     | Role                                                                                             |
|----------------------|--------------------------------------------------------------------------------------------------|
| MRI (pelvis) [15]    | Gold standard for assessing myometrial invasion, cervical stromal involvement, and nodal disease |
| CT abdomen/pelvis    | Used to evaluate extrauterine spread or distant metastases                                       |
| Chest X-ray/CT chest | To rule out lung metastases                                                                      |
| PET-CT               | Reserved for advanced or recurrent disease, or unclear findings on CT/MRI                        |

**Table 1.**  
*Imaging modalities in endometrial cancer.*

| Method                     | Details                                                                         |
|----------------------------|---------------------------------------------------------------------------------|
| Pipelle endometrial biopsy | First-line, outpatient, high sensitivity (~90%) for detecting carcinoma         |
| Dilation & Curettage (D&C) | Performed under anesthesia if biopsy is non-diagnostic or inadequate            |
| Hysteroscopy-guided biopsy | Gold standard for focal lesions or when fertility-sparing therapy is considered |

**Table 2.**  
*Methods to obtain biopsy in endometrial carcinoma.*

*Other specimen types include the following:*

Once diagnosed on biopsy, the standard operative procedure for EC is hysterectomy:

- Total hysterectomy: Removal of the uterus, including the cervix,
- Radical hysterectomy: Includes the parametria, upper vagina, and uterosacral ligaments. Surgeons should clearly indicate this on the histopathology requisition form when performed.

Surgical approaches may include laparoscopy, robot-assisted laparoscopy, or laparotomy. Minimally invasive methods can introduce the artifacts such as intravascular/intraluminal tumor fragments (e.g., in fallopian tubes) and myometrial clefts.

This clinical context is vital for accurate histopathological interpretation, determining tumor type, and guiding further management.

## **2.2 Macroscopic examinations include the following**

On receipt of specimen in the histopathology lab, proper orientation and prompt fixation (ideally within 1 hour of receiving the specimen) are essential to prevent autolysis and preserve molecular markers. The specimens are grossed as below [17]:

### **a. Uterus and tumor**

- Submit 1 section per 1 cm of maximal tumor dimension, or at least four blocks, including the area of deepest myometrial invasion [18].
- If no gross lesion is identified in a case with prior atypical hyperplasia or carcinoma, submit the entire endometrium and underlying myometrium.

### **b. Ovaries**

- Slice perpendicularly at 2–3-mm intervals [18],
- For non-endometrioid carcinomas: Submit entirely,
- For EEC: Submit at least 2 sections per ovary.

### **c. Fallopian tubes**

- For non-endometrioid carcinomas: Submit entirely using the SEE-FIM protocol [19].
- For EEC: Submit entire fimbriae and representative cross sections.

### **d. Omentum**

- Grossly inspect; section at 5-mm intervals [18].
- Sample:
  - Gross lesions: 1–2 blocks

- Grossly normal omentum: At least 4 sections or 1 per 2–3 cm of maximal dimension [20, 21]
- For optimal sensitivity (95%): Submit at least 10 sections.

## **2.3 Microscopic examination**

Microscopic evaluation begins with hematoxylin and eosin (H&E) staining, which provides an overview of the tumor architecture and cytological features. A detailed assessment of morphology—including glandular patterns, nuclear atypia, mitotic activity, and stromal invasion—is critical for accurate tumor classification.

When H&E findings are inconclusive or when further subtyping is required, relevant immunohistochemistry (IHC) plays a supportive role.

Accurate interpretation of morphology, supported by targeted IHC, ensures precise tumor classification and guides further prognostication and treatment planning.

Traditionally, endometrial carcinoma (EC) has been categorized into two groups according to the Bokhman classification, which considers clinical presentation, hormonal profile, and histopathological features as below [22]:

- Type I (endometrioid): Estrogen-dependent tumors, typically low-grade, arising in the setting of endometrial hyperplasia. These account for the majority of EC cases and generally have a favorable prognosis.
- Type II (non-endometrioid): Estrogen-independent, high-grade tumors (e.g., serous, clear cell, and undifferentiated carcinomas), often arising in an atrophic endometrium, with a more aggressive clinical course and poorer outcomes.

Although this dualistic model provided a useful clinical framework, it had notable limitations:

- Inconsistent reproducibility due to inter-observer variability, especially in high-grade tumors,
- Poor correlation with outcomes, leading to both over- and undertreatment,
- Limited biological insight, as it failed to reflect the underlying molecular diversity.

WHO 2022 classifies EC histologically as [23]:

Endometrioid carcinoma (EEC) of the uterine corpus,

Serous carcinoma (SC) of the uterine corpus,

Clear cell carcinoma of the uterine corpus (CCC),

Undifferentiated and dedifferentiated carcinomas of the uterine corpus (UDC/DDC),

Mixed carcinoma of the uterine corpus.

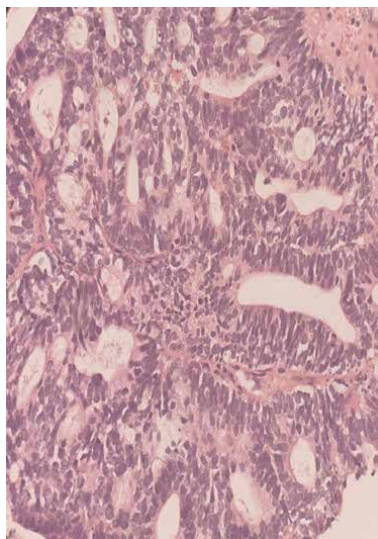
Other ECs: Mesonephric adenocarcinoma

- Squamous cell carcinoma NOS,
- Mucinous carcinoma, gastric (gastrointestinal)-type,
- Mesonephric-like adenocarcinoma.

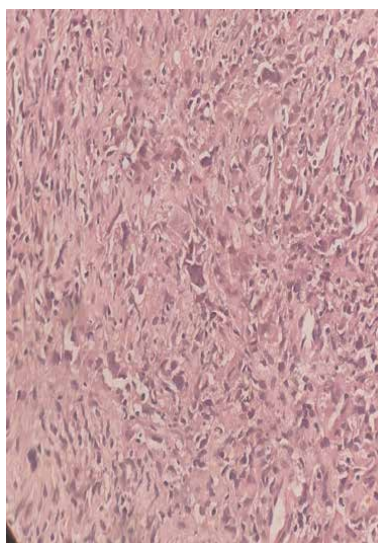
**Table 3** highlights the important features of different types of endometrial carcinoma:

| Feature               | EEC                                                                                                                                                                                                                                                                                                                        | SC                                                                                                                                   | CCC                                                                                                                                     | UDC/DDC)                                                                                                                                  |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| Age                   | PM; median ~ 63 years                                                                                                                                                                                                                                                                                                      | PM                                                                                                                                   | Mid to late 60s                                                                                                                         | Peri- PM; median ~ 55 years                                                                                                               |
| Clinical presentation | PMB; pelvic/abdominal pain in advanced cases                                                                                                                                                                                                                                                                               | PMB; often extrauterine spread (40–50%)                                                                                              | PMB; abnormal cervical cytology may occur                                                                                               | PMB; some with abdominal pain                                                                                                             |
| Epidemiology          | ~80–90% of EC                                                                                                                                                                                                                                                                                                              | ~10% of cases but ~40% of deaths                                                                                                     | Rare (<10% of ECs)                                                                                                                      | Rare (~2%); may be underrecognized                                                                                                        |
| Etiology              | Unopposed estrogen (obesity, nulliparity, PCOS, tamoxifen)                                                                                                                                                                                                                                                                 | Unknown                                                                                                                              |                                                                                                                                         |                                                                                                                                           |
| Risk Factors          | Estrogen exposure; Lynch and Cowden syndromes                                                                                                                                                                                                                                                                              | Multiparity, tamoxifen, prior radiation, BRCA mutations                                                                              | Possible increased risk of VTE; overlaps molecularly with SC and EEC                                                                    | Possible LS; dedifferentiation linked with MMRd and SWI/SNF complex loss                                                                  |
| Pathogenesis          | PTEN, PIK3CA, ARID1A, CTNNB1; MMRd, POLEmut, or NSMP                                                                                                                                                                                                                                                                       | TP53 mutations (universal); ERBB2 (HER2) amplification, PIK3CA, FBXW7, PPP2R1A                                                       | TP53 (36–59%), PIK3CA, PPP2R1A, KRAS, ARID1A, SPOP; MSI-H ~ 11–14%                                                                      | MMRd/MSI-H (~50–65%), PI3K pathway mutations; SWI/SNF gene loss (e.g. SMARCA4/SMARCB1); variable molecular subgroup                       |
| Macroscopy            | Exophytic/infiltrative masses; may have hemorrhage/ necrosis                                                                                                                                                                                                                                                               | Variable; invasive or polypoid mass                                                                                                  | Friable mass; no distinct gross features                                                                                                | Large polypoid intraluminal mass; necrosis common                                                                                         |
| Histology             | Glandular/villoglandular pattern; squamous differentiation in 10–25%<br>FIGO grading system:<br>• Grade 1: ≤5% solid growth<br>• Grade 2: 6–50% solid growth<br>• Grade 3: >50% solid growth<br>+1 grade if >50% cells show severe atypia<br>Binary grading: Grade 1–2 = low-grade, Grade 3 = high-grade (Figures 1 and 2) | Complex papillary/glandular, high-grade nuclei, psammoma bodies (Figure 3)                                                           | Tubulocystic, papillary, solid patterns; hobnail/ cuboidal cells; clear/ eosinophilic cytoplasm; no squamous differentiation (Figure 4) | Sheets of uniform discohesive cells; no glandular architecture; high mitotic rate; dedifferentiated forms include low-grade EEC component |
| IHC                   | ER+, PR+, variable PTEN, ARID1A, and MMR expression. (Figures 5–7)<br>Low-grade EEC: diffuse strong ER/PR, patchy p16 positivity. High-grade EEC: solid pattern, less nuclear pleomorphism than SC; loss of ARID1A, PTEN, or MMR favors high-grade EEC. Abnormal p53 expression in 2–5% low-grade and 20% high-grade EECs. | p53 mutant pattern (almost always), p16+, HER2 overexpression (~30%), ER/PR variable<br>WT1- (D/D tubo ovarian SC) (Figures 8 and 9) | HNF1β+, Napsin A+ (Figure 7b), AMACR +; ER/PR usually negative; p53 abnormal in 22–72% (Figure 10)                                      | Focal EMA/CK8/18+, dot-like; ER/PR negative; E-cadherin loss; SMARCA4/ SMARCB1 loss in ~50–60%; PAX8 focal/ negative                      |
| Prognosis             | Good (low grade/stage); depends on molecular subtype                                                                                                                                                                                                                                                                       | Poor; aggressive with high recurrence                                                                                                | Intermediate to poor; variable outcome                                                                                                  | Poor; aggressive clinical behavior                                                                                                        |

**Table 3.**  
*Clinicopathological characteristics in endometrial carcinoma.*



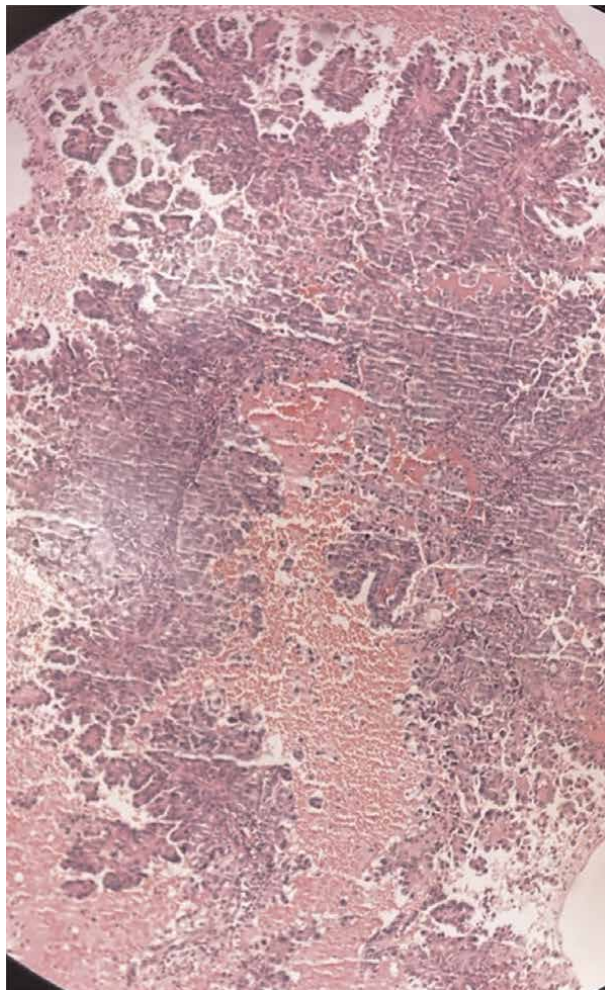
**Figure 1.**  
*Low-grade EEC (FIGO I) showing glandular pattern of tumor cells with <5% solid growth pattern.*



**Figure 2.**  
*High-grade EEC (FIGO III) showing marked cytological atypia with 80–90% non-squamous solid growth pattern.*

Following this histologic classification, the traditional management of endometrial carcinoma involved surgical staging TH-BSO and lymph node dissection—with adjuvant therapy decisions guided by the histopathological features.

While this approach remains clinically useful—especially for low-grade (FIGO grades 1 and 2) EEC, where diagnostic agreement is high—it suffers from significant interobserver variability in high-grade tumors, compromising prognostic accuracy and reproducibility.

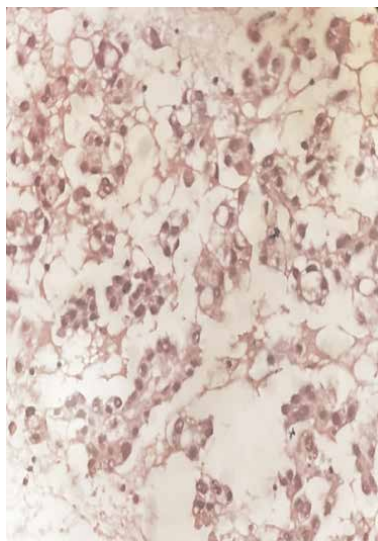


**Figure 3.**  
*Serous carcinoma showing predominantly complex papillary pattern of tumor cells.*

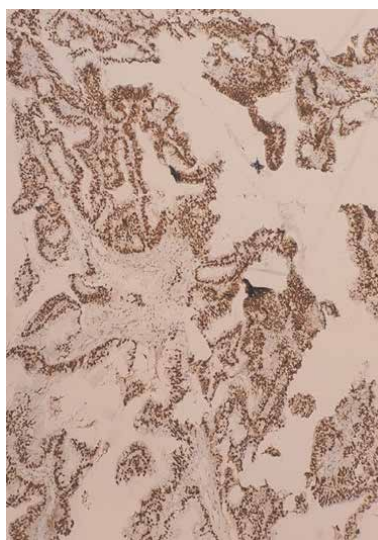
#### **2.4 The cancer genome atlas (TCGA)-based molecular classification**

TCGA 2013 performed an integrated genomic, transcriptomic, and proteomic analyses of ECs, revealing four biologically distinct molecular subgroups (**Table 4**) [7, 9].

Molecular classification thus plays a pivotal role in the management of EC by offering the prognostic, predictive, and therapeutic guidance. It refines risk stratification and informs decisions regarding the choice of adjuvant therapy (CT vs. RT), the use of immunotherapy (particularly in MMRd tumors), and fertility-sparing surgery eligibility. It also helps identify candidates for targeted therapies, such as PI3K/AKT/mTOR inhibitors in the selected NSMP tumors, and flags p53-abnormal tumors that often require treatment intensification due to poor prognosis. Incorporating these molecular markers into diagnostic workflows supports a more personalized and evidence-based approach to patient care.



**Figure 4.**  
*Clear cell carcinoma showing polygonal cells with moderate to abundant clear or eosinophilic cytoplasm.*

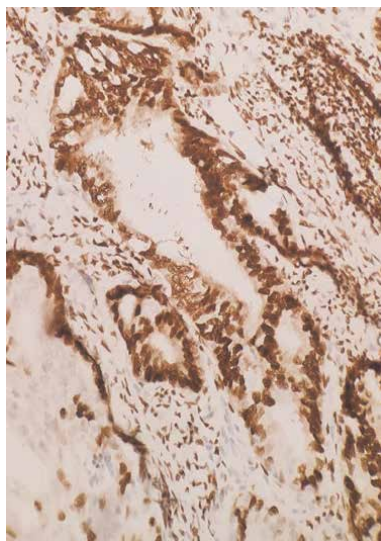


**Figure 5.**  
*Endometrioid carcinoma. Strong nuclear ER expression.*

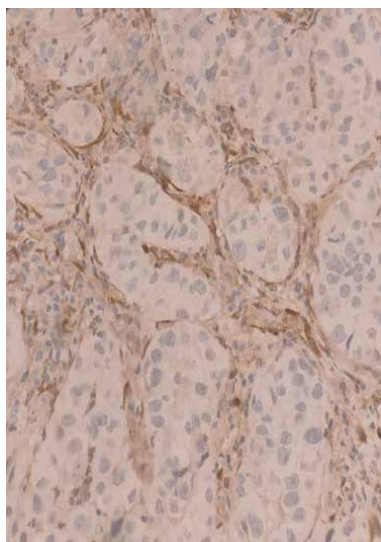
### 3. Molecular details

#### 3.1 Pole (DNA polymerase epsilon)

POLE encodes the catalytic subunit of DNA polymerase epsilon (Pol  $\epsilon$ ), the primary enzyme for leading strand DNA replication. Its high fidelity relies on accurate base incorporation and a 3'-5' exonuclease domain that removes the misincorporated nucleotides [24]. Mutations in the exonuclease domain impair this proofreading function,



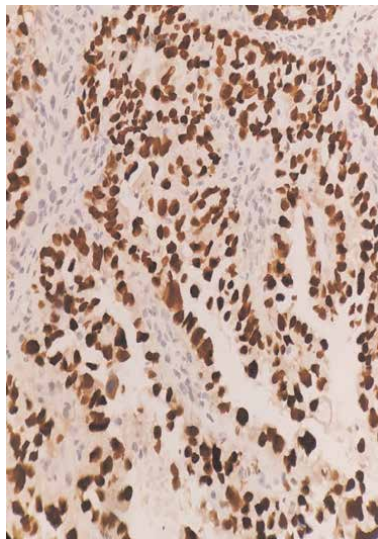
**Figure 6.**  
*Endometrial carcinoma. Strong nuclear PR expression.*



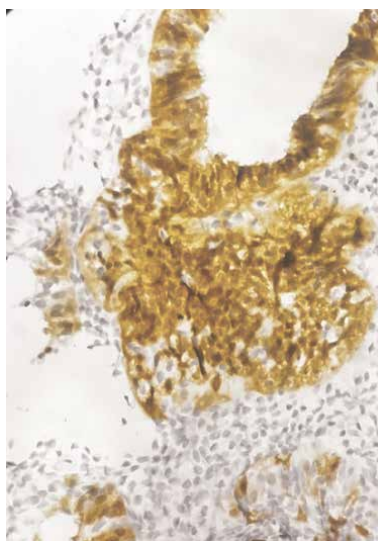
**Figure 7.**  
*Endometrial carcinoma. Loss of PTEN expression in the neoplastic cells.*

resulting in a dramatic increase in replication errors and an ultramutated tumor phenotype. Despite often presenting with high-grade histology, POLE-mutated tumors typically show strong immune infiltration and are associated with a favorable prognosis [25].

Similarly, POLD1 encodes the catalytic and proofreading subunit of DNA polymerase delta (Pol  $\delta$ ), primarily responsible for lagging strand synthesis, but also capable of contributing to leading strand replication [25]. Mutations in its exonuclease



**Figure 8.**  
*Serous carcinoma. Strong and diffuse nuclear expression of p53 (overexpression) in tumor cells.*

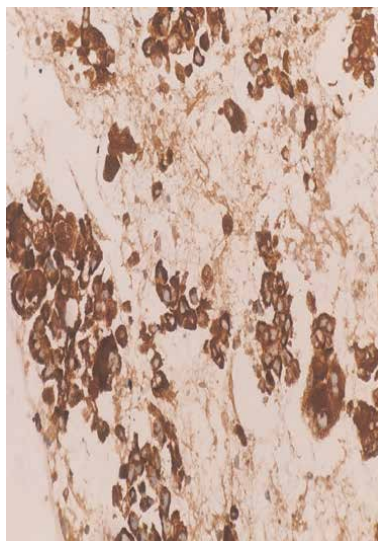


**Figure 9.**  
*Serous carcinoma. Diffuse p16 expression in 60–70% of tumor cells.*

domain, though less common, can also result in a hypermutated phenotype and have been linked to EC [26].

Both Pol  $\epsilon$  and Pol  $\delta$  contain intrinsic proofreading domains that are essential for maintaining genomic stability by correcting replication errors [27, 28].

In the TCGA EC cohort, a total of 530 tumors were analyzed. Among these, 82 tumors harbored somatic POLE mutations, and of these, 59 mutations were located within the EDM [29].



**Figure 10.**  
*Clear cell carcinoma. Cytoplasmic granular Napsin A expression in tumor cells.*

To identify truly pathogenic POLE EDMs EC, a POLE scoring system was developed based on five genomic features associated with known hotspot mutations [29]:

- TMB >100 mut/Mb
- C > A  $\geq$  20%
- T > G  $\geq$  4%
- C > G  $\leq$  0.6%
- Indels  $\leq$  5%

Each criterion contributes to one point; a score of  $\geq 4$  defines pathogenic mutations,  $\leq 2$  indicates non-pathogenic variants, and a score of 3 represents variants of uncertain significance (VUS). Recurrent mutations were also factored into the score.

In the TCGA cohort, only 11 of 21 POLE-EDM variants (**Table 5**) met the threshold for pathogenicity, demonstrating that not all POLE mutations—even within the exonuclease domain—are clinically significant. This highlights the inadequacy of using mutation presence alone to guide classification or treatment [29–31].

These 11 discrete pathogenic variants are as follows [31]:

Of these, two P286R and V411 are present in approximately two thirds of POLE mutant EC, and 5 “hotspots” with additional S297F, A456P, and S459F cover the vast majority.

These are concentrated, with around 90% occurring in exons 9 and 13, which are critical for proofreading function and are thus classified as pathogenic [32].

These mutations typically reside within or adjacent to conserved exo-motif regions, where they disrupt the DNA interaction interface, thereby eliminating

| Feature                       | POLE-ultramutated (POLEmut)                                                                                                        | MMR-deficient (dMMR/MSI-H)                                                                                  | No Specific Molecular Profile (NSMP)                                                                                                                                                     | Copy-Number High/p53-abnormal (CNH)                                                                                                                                                                             |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Key Features                  | POLE exonuclease domain mutations → ultrahigh mutation burden (Ultramutated ( $\geq 100$ mut/Mb)); strong lymphocytic infiltration | Defects in MMR proteins; hypermutation (10–100 mut/Mb); immune infiltration; MLH1 promoter hypermethylation | Microsatellite stable; heterogeneous histology                                                                                                                                           | Genomic instability; frequent copy-number alterations                                                                                                                                                           |
| Clinical features             | Younger<br>Low BMI<br>Early stage                                                                                                  | LS associated<br>High BMI<br>Local recurrence                                                               | High BMI                                                                                                                                                                                 | Older<br>Low BMI<br>Advanced stage                                                                                                                                                                              |
| Frequency                     | ~7–12%                                                                                                                             | ~25–30%                                                                                                     | ~39%                                                                                                                                                                                     | ~15%                                                                                                                                                                                                            |
| Histological Features         | High-grade; ambiguous morphology; tumor giant cells; prominent TILs & TLS                                                          | Often high-grade; mucinous differentiation; MELF pattern; substantial LVSI; TILs & TLS                      | Mostly low-grade EEC with squamous differentiation or morules                                                                                                                            | High-grade SC; diffuse cytonuclear atypia; glandular/solid patterns; substantial LVSI                                                                                                                           |
| Molecular Markers/Alterations | POLE exonuclease domain mutations (exons 9, 13, 14); high TMB                                                                      | Loss of MMR; MSI-H                                                                                          | PTEN, PIK3CA, CTNNB1 ( $\beta$ -catenin exon 3); ER/PR+                                                                                                                                  | TP53 mutations, frequent HRD                                                                                                                                                                                    |
| Diagnostic tests              | NGS/Sanger/hotspot qPCR/hotspot analysis includes p.Pro286Arg, p.Val411Leu, p.Ser297Phe, p.Ala456Pro, and p.Ser459Phe              | MMR IHC; MSI testing by NGS                                                                                 | CTNNB1 mutation analysis/ $\beta$ catenin IHC                                                                                                                                            | p53- IHC (mutant-like pattern)/ NGS                                                                                                                                                                             |
| Treatment                     | TH-BSO and observation<br>EBRT when indicated<br>ICI in advanced and recurrent<br>De-escalation of therapy/ no CT                  | RT<br>Eligible for ICI (pembrolizumab, dostarlimab);<br>LS screen                                           | TH + BSO<br>With LN assessment<br>+risk-adapted adjuvant therapy;<br>CT $\pm$ RT<br>RT $\pm$ ET<br>Immunotherapy (e.g., pembrolizumab with lenvatinib) in advanced and recurrent of pMMR | Requires CT (carboplatin and paclitaxel) $\pm$ RT; HER2-targeted therapy (if HER2+) may be beneficial<br>Immunotherapy (e.g., pembrolizumab with lenvatinib) in advanced and recurrent<br>Escalation of therapy |
| Potential prognostic markers  |                                                                                                                                    | TLS<br>MLH1 promoter methylation vs. germline mutations)                                                    | TIL<br>CTNNB1+, L1CAM+ and ER- = high risk                                                                                                                                               | TIL                                                                                                                                                                                                             |
| Prognosis                     | Excellent                                                                                                                          | Intermediate                                                                                                | Intermediate                                                                                                                                                                             | Poor                                                                                                                                                                                                            |

**Table 4.**  
*Molecular classification of endometrial carcinoma.*

exonuclease activity. This functional loss compromises replication accuracy, significantly contributing to mutation accumulation and tumor progression [28].

Although the POLE score provides a useful framework, it remains unvalidated in large, independent cohorts and is not yet an internationally accepted tool for treatment decisions. Historically, only the five most common hotspot mutations have been used in survival analyses and clinical trials, such as PORTEC-3 [31, 33].

However, a meta-analysis of 294 POLEmut ECs, including the 11 pathogenic variants, showed a low recurrence rate of 3.7%, though one patient had both P286R and V411L mutations [31].

The ongoing RAINBO-POLEmut-BLUE trial (NCT05255653) is the first prospective study to explore adjuvant therapy omission or de-escalation in POLEmut EC, using these 11 pathogenic variants to define eligibility. Its results will help determine which mutations safely allow for less intensive treatment [34].

Also, it has not been determined as yet the effect that rarer non-hotspot variants in POLE will have on the tumor's biology. As whole-genome/exome sequencing becomes more common, more pathogenic POLE variants are likely to be identified. However, robust evidence will be needed before incorporating new variants into clinical decision-making frameworks for prognosis or treatment de-intensification [29, 31].

### 3.1.1 POLE mutation testing

Currently, POLE mutations are primarily detected *via* targeted sequencing (e.g., of exons 9, 13, 14 or 9–14) using Sanger sequencing and next-generation sequencing (NGS) [31]. However, Sanger sequencing may yield false-negative results due to preferential amplification of the wild-type allele. While NGS provides high accuracy, it is costly, time-consuming and requires specialized personnel for data interpretation. As a result, alternative, more accessible testing methods are under investigation [35].

| Mutation | cDNA change      |
|----------|------------------|
| P286R    | c.857C > G       |
| V411L    | c.1231G > T or C |
| S297F    | c.890C > T       |
| S459F    | c.1376C > T      |
| A456P    | c.1366G > C      |
| F367S    | c.1100 T > C     |
| L424I    | c.1270C > A      |
| M295R    | c.884 T > G      |
| P436R    | c.1307C > G      |
| M444K    | c.1331 T > A     |
| D368Y    | c.1102G > T      |

**Table 5.**  
*Variants of POLE-EDM.*

- QPOLE, proposed by Van den Heerik et al., is a quantitative PCR-based approach involving three assays [36]:
- QPOLE-frequent detects the five most common variants (P286R, V411L-T/C, S297F, A456P, S459F).

QPOLE-rare-1 and QPOLE-rare-2 identify the rarer mutations (M295R, F367S, D368Y, L424I, M444K, and P436R).

QPOLE demonstrates 98.6% concordance with NGS, which is faster, less expensive, and potentially easier to implement clinically. A stepwise approach—starting with QPOLE-frequent and extending to rare assays as needed—has been proposed [35, 36].

Droplet digital PCR (ddPCR) has also shown promise in detecting the five most frequent POLE pathogenic variants. Although it appears cost-effective and practical, current studies are limited by small sample sizes, warranting further validation [35, 37].

BaseScope, an *in situ* hybridization (ISH) technique for POLE mRNA, has been introduced by Yu et al. It successfully detected P286R and V411L mutations with high sensitivity (95%) and specificity (100%) using dual probes. However, its applicability to other POLE variants remains under investigation [35, 38].

No immunohistochemical test exists for detecting POLE exonuclease domain mutations.

### 3.2 MMR system

The MMR system is a conserved DNA repair pathway that corrects base mismatches and small insertions/deletions during replication along with POL. The 4 MMR proteins form heterodimers: [39].

- MSH2 + MSH6 = MutS $\alpha$
- MSH2 + MSH3 = MutS $\beta$
- MLH1 + PMS2 = MutL $\alpha$
- MLH1 + PMS1 = MutL $\beta$
- MLH1 + MLH3 = MutL $\gamma$

MLH1 and MSH2 are stable on their own and act as driver proteins, while PMS2 and MSH6 depend on their partners for stability. Loss of the driver protein MLH1 or MSH2 leads to loss of both dimer partners' expression, whereas the isolated loss of PMS2 or MSH6 suggests the direct mutation in those genes [40].

MMR deficiency (MMRd) results from germline or somatic mutations in these four genes, MLH1 promoter hypermethylation or EPCAM deletions (rare) [41].

Microsatellite instability (MSI): MMRd leads to errors in repetitive DNA sequences (microsatellites), causing microsatellite instability (MSI). MSI testing involves

comparing repeat lengths at standard markers (BAT25, BAT26, D2S123, D5S346, and D17S250) in tumor vs. normal DNA [42]:

- MSI-High (MSI-H):  $\geq 2$  markers unstable,
- MSI-Low (MSI-L): 1 unstable marker,
- Microsatellite Stable (MSS): No instability.

### *3.2.1 MMR IHC testing and interpretation*

The concordance between MMR IHC and microsatellite instability analysis is high (93–95%) [30, 43]. IHC is a cost-effective and widely used method to screen for MMR deficiency and indirectly detect microsatellite instability (MSI), as endorsed by the ISGyP guidelines [44].

Normal IHC: Uniform, strong nuclear staining in tumor cells (MLH1, PMS2, MSH2, and MSH6) compared to internal controls (e.g., stromal cells) [45].

Abnormal IHC: Loss of expression denotes the absence of nuclear staining in tumor cells and should only be reported if internal control cells are positive. Partial or weak staining should prompt re-evaluation or molecular testing. Aberrant expression patterns include cytoplasmic, nucleolar, or punctate nuclear staining, and should not be interpreted as intact expression [46].

IHC loss patterns and likely cause: [30].

- MLH1/PMS2 loss  $\rightarrow$  MLH1 promoter hypermethylation  $\rightarrow$  if -nt, genetic counseling,
- MSH2/MSH6 loss  $\rightarrow$  MSH2 mutation (or rarely MSH6)  $\rightarrow$  if -nt, genetic counseling,
- Isolated PMS2 loss  $\rightarrow$  PMS2 mutation  $\rightarrow$  genetic counseling,
- Isolated MSH6 loss  $\rightarrow$  MSH6 mutation  $\rightarrow$  genetic counseling.

IHC may yield non-informative results due to pre-analytical issues like poor fixation.

Subclonal loss of MMR protein expression—where only focal areas of the tumor lack staining—can complicate diagnostic interpretation. Such cases may require repeat IHC with all 4 IHC markers or MSI testing, especially when LS is suspected as some germline mutations do not affect protein expression [47, 48]. Discordance between IHC and MSI status may result from the technical factors, missense mutations, or non-classical pathways of instability. Subclonal loss of MLH1/PMS2 or MSH6, reported in about 7% of EECs, can result from MLH1 promoter hypermethylation or POLE mutations and rarely occurs in LS-associated tumors. Hence, even focal staining should not be interpreted as definitively intact and must be correlated clinically [49].

Testing for MMR/MSI status in EC is important for four key reasons:

1. Diagnostic—MMRd/MSI-H supports a diagnosis of EEC over SC or HPV-associated cervical carcinoma [50].

2. Screening—It aids in identifying patients at risk for LS, enabling risk-reducing strategies for affected patients and also allows for cancer prevention and early detection in at-risk family members [51].
3. Prognostic—MMR status contributes to risk stratification within the TCGA molecular classification [52].
4. Therapeutic—MMRd / MSI-H serves as a predictive biomarker for response to Immune checkpoint inhibitors (ICI) [53].

Approximately 3% of all ECs—and about 10% of MMRd or MSI-H tumors—are linked to germline mutations in MMR genes or EPCAM.

### **3.3 p53 mutation**

p53 is a tumor suppressor protein that plays a critical role in regulating cell proliferation, DNA repair, apoptosis, and maintaining genomic stability [54]. Its inactivation can occur either through mutations in the TP53 gene or through functional deactivation, such as binding by viral oncoproteins like HPV E6 [55]. These alterations lead to dysregulated cellular growth. Mutant p53 protein accumulates abnormally in tumor cells, and this aberrant expression can be tested using IHC (**Table 6**).

Problematic areas in p53 IHC interpretation are highlighted in **Table 7** [56–58].

There are interlaboratory variations in p53 IHC protocols, with the DO-7 clone demonstrating the most reliable performance and highest interobserver agreement. While expert pathologists generally show strong concordance in interpreting p53 IHC on biopsy specimens, less experienced pathologists may require additional familiarity with abnormal staining patterns. Interpretation can be compromised by technical issues such as suboptimal antigen retrieval, use of aged tissue sections, or inadequate fixation. Additionally, some tumors may exhibit enhanced staining that does not meet the threshold for overexpression, leading to interpretive ambiguity. In such cases, it is advisable to reassess both biopsy and resection specimens and consider TP53 gene sequencing when uncertainty persists.

### **3.4 PD1/PDL1**

PD-L1 is expressed in up to one-third, and PD-1 in up to 50%, of pMMR/MSS cases—suggesting PD-L1 testing could help identify candidates for ICI monotherapy [59]. The DUO-E trial further demonstrated improved progression-free survival (PFS) in PD-L1–positive pMMR/MSS patients when durvalumab was combined with the PARP inhibitor olaparib, highlighting the value of PD-L1 assessment for tailoring advanced EC treatment [60].

## **4. Stepwise molecular testing algorithm for EC**

While full molecular typing has predictive value, it lacks broad clinical validation. The TCGA-surrogate algorithm recommended by the International Society of Gynecological Pathologists (ISGyP) also known as Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), endorsed by the WHO, and the independently validated TransPORTEC classifier are more widely adopted and utilizes three immunohistochemical markers (p53, MSH6, and PMS2) and one molecular test (POLE

| p53 IHC pattern         | Interpretation | TP53 mutation type                                                                                         | % in HGSC | Concise notes                                                                                                                                                        |
|-------------------------|----------------|------------------------------------------------------------------------------------------------------------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Wild type (Normal)      | Normal         | No mutation                                                                                                | 0%        | Nuclear staining ranges from few to almost all tumor cells, but with variable intensity; stromal fibroblasts and intratumoral lymphocytes act as intrinsic controls. |
| Overexpression          | Abnormal       | Nonsynonymous (missense); also in-frame deletions, splicing                                                | 66%       | Strong nuclear staining in $\geq 80\%$ of tumor cells; due to impaired degradation via MDM2; most common pattern in HGSC.                                            |
| Complete absence (Null) | Abnormal       | Indels, stop gains, splicing mutations                                                                     | 25%       | No tumor nuclear staining; internal control positive; due to nonsense-mediated mRNA decay from truncating mutations.                                                 |
| Cytoplasmic             | Abnormal       | Indels and stopgains disrupting nuclear localization domain                                                | 4%        | Predominant cytoplasmic staining; weak or absent nuclear staining; rare pattern.                                                                                     |
| Wild type (Normal*)     | Normal*        | Truncating mutation (non-functional but stable protein)                                                    | 5%        | Mutated TP53 but IHC appears wild type; may require sequencing for clarification.                                                                                    |
| Subclonal               | Abnormal       | early mutation or artifact, secondary mutational event in the setting of MMR-d or POLEm in mixed carcinoma | 21%       | Any abnormal pattern (overexpression, null, cytoplasmic) present only in a subset of tumor cells, $<10\%$                                                            |

*About 5% of HGSCs show a normal (wild-type) p53 IHC pattern despite carrying TP53 mutations. These are typically truncating mutations that create a shortened protein still detectable by most N-terminal-targeted antibodies*

**Table 6.**  
*Reporting p53 Status by IHC [56, 57].*

mutation analysis) to stratify endometrial cancers into four molecular subtypes. This approach is especially useful in high-grade EEC, allowing distinction between favorable POLEmut tumors and poor-prognosis p53abn tumors, with MMRd and NSMP showing intermediate outcomes [44].

Molecular classification is recommended for all endometrial carcinomas and can be done on biopsy, curettage, or hysterectomy specimens. Performing it early on biopsy material may guide surgical management decisions.

Standard testing algorithm (ideal settings) [61, 62]:

1. Start with POLE mutation testing (sequencing)
  - If POLE-mutated:
    - Excellent prognosis (regardless of grade or stage)
    - Eligible for treatment de-escalation
    - Minimal or no adjuvant therapy may be needed

| Pattern being compared            | Issue                          | Description/Interpretation Clue                                                                                          |
|-----------------------------------|--------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| 1. Wild type vs. Overexpression   | 1a. High wild type             | Strong nuclear staining in <80% cells; high proliferation; use intrinsic control as guide.                               |
|                                   | 1b. Low overexpression         | Weak overall staining; >80% nuclei stain (some weakly/negatively); may mimic wild type; “mosaic” pattern possible.       |
|                                   | 1c. Heterogeneous staining     | More than one staining pattern; rare in HGSC (<3%); due to fixation delay or complex mutation effects; report if seen.   |
| 2. Wild type vs. Complete Absence | 2a. Low wild type staining     | Low proliferation or antigen degradation; weak/absent staining; can mimic null.                                          |
|                                   | 2b. Lack of intrinsic control  | No staining in both tumor and stromal/lymphocytes; unreliable interpretation; do not report absence without control.     |
|                                   | 2c. Occasional tumor staining  | Rare positive nuclei in mostly negative tumor; not true null; suggestive of technical or biological variation.           |
|                                   | 2d. True wild type HGSC        | Very rare (<5%); mutation may be present but IHC appears wild type; consider molecular testing if needed.                |
| 3. Wild type vs. Cytoplasmic      | 3a. Threshold not well defined | Diagnosis of cytoplasmic pattern requires clear predominance and moderate intensity; avoid overcalling weak cytoplasm.   |
|                                   | 3b. Spurious cytoplasmic stain | Should not be seen in normal cells; background cytoplasmic stain may confuse interpretation; nuclear stain usually weak. |

**Table 7.**  
*Pitfalls in interpretation of IHC expression.*

2. If POLE wild-type, perform MMR IHC

- If MMR-deficient (loss of MLH1, MSH2, MSH6, PMS2):
  - MMRd group
  - Consider LS testing
  - Eligible for immunotherapy in advanced/recurrent settings

3. If MMR-proficient, perform p53 IHC

- If p53 abnormal (strong diffuse staining or complete loss):
  - p53abn group
  - Poor prognosis, may need aggressive multimodal therapy

4. If p53 normal (wild-type):

- NSMP
- Intermediate risk; stratify further with ER status, LVSI, and CTNNB1 mutation if available.

While the algorithm was originally developed for EC and SC, its application to other histologic subtypes—such as CCC, UDC/DDC, neuroendocrine carcinoma, and carcinosarcoma—is possible, though currently limited by available data, as these were not included in the original TCGA study [31, 63]. Nonetheless, preliminary evidence supports its potential value in these rare tumor types.

There are two additional complexities to POLE testing: distinguishing between pathogenic and non-pathogenic mutations, and coexistence of ultramutation (i.e., pathogenic POLE mutation) with secondary mutations in TP53 and/or one or more of the MMR genes. These “multiple classifier” cases are currently thought to retain the favorable prognosis of POLE-mutated tumors, regardless of MMR or p53 status but this is still an evolving field. Prognosis thus aligns with the dominant driver (e.g., POLEmut overrules p53abn) [29, 31, 64].

Classifier hierarchy of POLE > MMRd > p53-abn > NSMP is used when overlapping profiles occur.

#### **4.1 Modified approach for low-resource settings**

In settings where comprehensive molecular testing is not feasible, a selective Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) classifier, developed through the Molecularly Informed Endometrial Cancer Care (MoLIInEC) initiative, may be adopted in routine practice [45, 65]. According to this modified strategy, MMR and p53 IHC are performed for all cases, while POLE mutation testing is reserved only for those patients in whom POLE status would influence adjuvant treatment decisions [35]. This stepwise, IHC-based approach continues to provide clinically meaningful risk stratification, even in resource-limited settings [62].

1. Start with MMR IHC (widely available and cost-effective)
  - If MMR-deficient:
    1. Classify as MMRd
    2. Evaluate for LS; consider ICB in advanced cases
2. If MMR-proficient, perform p53 IHC
  - If p53 abnormal:
    - Classify as p53abn → high-risk; aggressive treatment needed
3. If p53 normal (wild-type):
  - Classify as NSMP
  - Use clinicopathologic features (grade, LVSI, ER status) for treatment planning
4. POLE mutation testing (optional/if available):
  - Reflex to POLE sequencing only if clinicopathologic features suggest a need for further risk refinement (e.g., early-stage, high-grade, ER-positive NSMP with no LVSI).

- If mutated:
  - Reclassify as POLE-ultramutated
  - Excellent prognosis; may omit or reduce adjuvant therapy.

This flexible algorithm enables molecular-guided management of EC across a wide range of clinical settings, aligning treatment intensity with biologic risk even in constrained environments.

Other strategies were to decrease the cost of POLE sequencing in routine endometrial cancer diagnostics, especially for broader implementation in low- and middle-income settings:

1. Use of targeted gene panels: Instead of whole-exome or multigene sequencing, employ small, focused panels that include only key hotspots in the POLE exonuclease where >95% of pathogenic mutations occur. This drastically reduces sequencing cost and data analysis burden [66].
2. Pooled testing/barcoded multiplexing: Multiple samples can be pooled and barcoded in a single sequencing run to reduce per-sample cost. Particularly effective in high-volume centers where multiple EC samples are sequenced simultaneously [67].
3. Sanger sequencing in selected cases: In centers without NGS access, Sanger sequencing of exons 9, 13, and 14 of POLE can be a low-cost alternative. This is feasible when molecular testing is limited to select histologic subgroups (e.g., high-grade EEC) [35].
4. Integration with institutional or national cancer genomic initiatives: Join national genomic consortia or academic collaborations that subsidize or bulk-negotiate sequencing costs [68].
5. Development of low-cost PCR-based assays: Ongoing research is creating PCR-based mutation-specific assays to detect common POLE hotspot mutations (e.g., P286R, V411L). These can be implemented on existing hospital PCR platforms, avoiding the need for NGS [37].
6. Advocacy for insurance or government reimbursement: Include POLE testing as a standard-of-care recommendation in national clinical guidelines to support policy change and reimbursement [69].

## **5. Guidelines supporting molecular integration**

There is ongoing debate about whether molecular classification should be applied universally to all ECs or limited to diagnostically challenging high-grade tumors. Key concerns include the predominantly retrospective nature of current evidence, with prospective validation still pending (e.g., RAINBO trial) [34]. Additionally, limited access to resources, especially for POLE mutation testing, poses practical challenges. Most supporting data for TCGA-based classification come from two large retrospective cohorts [29, 31].

International guidelines increasingly support integrating molecular classification into routine evaluation and management of EC, particularly in high-grade or early-stage cases.

- WHO (2022): Recommends routine testing for POLE mutations, MMR deficiency, and p53 abnormalities as part of an integrated histologic-molecular approach, especially in high-grade tumors [23].
- ESGO/ESTRO/ESP (2021): Endorse universal MMR testing and selective POLE and p53 IHC based on risk groups, to guide adjuvant therapy decisions [70].
- ESMO: Aligns with near-universal MMR testing and emphasizes molecular profiling (especially POLE) for prognostic and therapeutic guidance [71].
- NCCN: Advises universal LS screening (*via* MMR IHC or MSI testing) and recommends POLE/p53 testing in the selected cases to refine prognosis and tailor treatment [72].
- SGO: Supports universal MMR testing and encourages broader use of molecular subtyping (MMR, p53, POLE), particularly in research and increasingly in clinical practice [73].
- Isgyp, SITC, and Manchester International Consensus Group: Supports universal MMR testing as a significant number of women with LS are missed by clinical screening based solely on personal and family history, as up to 75% do not meet the revised Bethesda Guidelines [44].

Together, these guidelines mark a shift toward precision medicine in EC, enabling the individualized risk assessment and treatment planning.

Recent clinical trials are increasingly applying molecular classification to refine adjuvant therapy in endometrial carcinoma (EC). The PORTEC-4a trial is evaluating the role of molecular profile-based adjuvant RT versus standard treatment in early-stage EC, with study completion expected by December 31, 2028. The TAPER trial focuses on patients with POLE-mutated and p53 wild-type/NSMP tumors, investigating the potential for de-escalated adjuvant therapy in this favorable-risk subgroup, with completion anticipated by June 30, 2029. The results of these two trials are expected to clarify whether molecular profiling can reliably guide adjuvant treatment decisions, potentially reducing overtreatment and improving patient outcomes [74, 75].

## **6. Reporting of EC on histopathology**

### **6.1 Diagnostic pathway for endometrial biopsy reporting**

1. PMB → TVUS
2. Endometrial thickness > 4 mm → Pipelle biopsy
3. Non-diagnostic biopsy or focal lesion → Hysteroscopy/D&C
4. Confirmed EC → MRI for staging + MMR, p53, POLE testing
5. Multidisciplinary team (MDT) planning for surgery/treatment [9]

## 6.2 Reporting of endometrial resection specimens

The histopathology report for EC should include status on [62]:

- Histological subtype (e.g., EEC, SC, CCC)
- Tumor grade (G1–G3)
- Depth of myometrial invasion
- LVSI
- Cervical involvement

Thereafter molecular classification can be integrated into diagnostic protocols using:

- POLE sequencing
- MMR IHC (for LS screening and classification)
- p53 IHC

## 6.3 Staging

The 2023 FIGO staging system supports the integration of complete molecular classification in all ECs to enhance prognostic risk stratification and guide adjuvant/systemic treatment decisions [9].

While not mandatory for staging, POLE mutations and p53 abnormalities can result in upstaging or downstaging of stage I and II tumors, indicated by adding an “m” to the FIGO stage (e.g., IA<sub>m</sub>), with subscripts denoting molecular subtype (e.g., POLE mut or p53abn). In stages III–IV, molecular data do not change the stage but should be documented for decision-making and research purposes [9].

The FIGO 2023 staging system introduces refined criteria for EC, improving prognostic accuracy and guiding individualized treatment, particularly in early-stage disease. While the staging remains anatomically based, it now formally incorporates LVSI and histologic subtype into sub-staging, with molecular classification used to inform treatment—though not part of the stage label [9, 76].

Key features of FIGO 2023 staging (**Table 8**) [9]:

- Subdivided stages I and II based on myometrial invasion, LVSI, and tumor histology,
- LVSI and aggressive histotypes (e.g., SC, CCC) influence stage assignment,
- Molecular markers (e.g., POLE, MMRd, p53abn) guide adjuvant therapy but are not included in formal stage designation.

Overall, the updated FIGO system promotes a risk-adapted, integrated approach, combining anatomic, histologic, and molecular factors to better guide prognosis and individualize adjuvant therapy.

| Stage I  | Tumor Confined to the Corpus Uteri                               |
|----------|------------------------------------------------------------------|
| Substage | Criteria                                                         |
| IA1      | <50% myometrial invasion, no LVSI, non-aggressive histology      |
| IA2      | <50% myometrial invasion, LVSI present, non-aggressive histology |
| IA3      | <50% myometrial invasion, aggressive histology eg. serous        |
| IB       | ≥50% myometrial invasion, no LVSI, non-aggressive histology      |
| IC       | ≥50% myometrial invasion with LVSI or aggressive histology       |
| Stage II | Cervical Stromal Invasion                                        |
| Substage | Criteria                                                         |
| IIA      | <50% myometrial invasion + cervical stromal invasion             |
| IIB      | ≥50% myometrial invasion + cervical stromal invasion             |
| IIC      | Cervical stromal invasion with LVSI or aggressive histology      |

**Table 8.**  
*FIGO staging, 2023 for endometrial carcinoma.*

## 7. Treatment decision based on risk stratification

Treatment of EC is increasingly guided by an integrated risk stratification approach (**Table 9**), combining clinicopathologic features (e.g., stage, grade, histology, LVSI) with molecular classification. This allows for personalized, risk-adapted therapy that avoids overtreatment in low-risk cases and ensures adequate management in high-risk disease [30, 77].

Risk-adapted treatment in EC now reflects a shift from traditional histology-based decisions to a biologically informed model, allowing for precision therapy tailored to the tumor’s behavior and molecular profile [78].

## 8. Prognostic factors

The prognosis of EC depends on a combination of clinicopathological and molecular factors (**Table 10**) [79].

## 9. Challenges and future directions

Despite significant advances in the molecular understanding of EC, several challenges continue to limit optimal outcomes [80–82]:

- Rising incidence driven by aging and obesity,
- Persistent mortality rates, especially in advanced or aggressive subtypes,
- Limited therapeutic options for chemo-resistant and high-risk molecular groups,
- Disparities in access to genomic testing, molecular diagnostics, and novel therapies,

| Risk group                | Criteria                                                                  | Molecular notes                                                        | Management                                                                                     |
|---------------------------|---------------------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| 1. Low-risk               | Stage IA, low-grade EEC, no LVSI, POLE mut or NSMP                        | POLE mut associated with excellent prognosis                           | Surgery alone (TH ± BSO); no adjuvant therapy                                                  |
| 2. Intermediate-risk      | Stage IA–IB, low-grade EEC, focal LVSI or NSMP                            | MMRd supports observation in early disease; consider ICI in recurrence | Surgery + vaginal brachytherapy may be considered                                              |
| 3. High-intermediate risk | Stage IB or early Stage II, LVSI present, Grade 2–3, NSMP or MMRd         | POLE mut in this group may avoid adjuvant therapy                      | Surgery + adjuvant RT (EBRT ± brachytherapy)                                                   |
| 4. High-risk              | SC, CCC, Grade 3 EEC with deep invasion or extensive LVSI; p53abn subtype | p53 abn tumors benefit from combined chemoradiation                    | Surgery + adjuvant CT and/or RT                                                                |
| 5. Advanced/recurrent     | Advanced stage or recurrent disease                                       | Molecular testing essential to guide systemic therapy decisions        | MMRd/MSI-H → ICI (pembrolizumab, dostarlimab)<br>pMMR → Lenvatinib + pembrolizumab<br>HR+ → HT |

**Table 9.**  
*Risk stratification of endometrial carcinoma.*

- Underutilization of fertility-sparing treatments in eligible young patients,
- High costs and inconsistent availability of molecular testing across regions,
- Complexity in interpreting molecular variants, such as POLE VUS,
- Lack of integration between molecular profiles and traditional clinical or radiologic staging,
- Absence of standardized protocols for molecular testing and treatment decision-making.

| Category              | Prognostic indicator                                     |
|-----------------------|----------------------------------------------------------|
| Stage                 | Most critical; early-stage (I–II) = better prognosis     |
| Grade                 | High-grade tumors are more aggressive                    |
| Histology             | Serous, clear cell, and carcinosarcoma = worse outcomes  |
| Myometrial invasion   | Deep invasion correlates with lymphatic spread           |
| LVSI                  | Strongly linked to recurrence and nodal involvement      |
| Molecular subtype     | POLE-mutated = excellent; p53abn = poor prognosis        |
| Age and comorbidities | Older age and obesity are associated with worse outcomes |

**Table 10.**  
*Key prognostic factors in endometrial carcinoma.*

In response to these challenges, future directions are focused on transforming EC care through:

1. Molecular integration into clinical practice: TCGA-based molecular classification (POLE-mutated, MMRd, NSMP, and p53-abnormal) is now central to risk-adapted treatment planning. POLE-mutated tumors have an excellent prognosis and may be spared adjuvant therapy, while p53-abnormal tumors are aggressive and require intensive management. Within the heterogeneous NSMP group, L1CAM overexpression and ER-negativity further stratify patients with high recurrence risk and poorer outcomes, highlighting the need for more nuanced molecular profiling [33, 61, 77].
2. Expansion of immunotherapy: ICI are effective in MMRd and MSI-H tumors. However, immune response appears to be driven more by tumor microenvironment than by molecular subtype alone. The presence of tertiary lymphoid structures (TLS) is emerging as a superior biomarker of immunogenicity and prognosis, even in subtypes like NSMP and p53-abnormal, and may better predict immunotherapy response in future protocols [83]. Expression of PD-L1 and PD-1 could broaden the applicability of ICIs in pMMR/MSS endometrial cancer. Continued investigation is essential to define their clinical relevance and enhance the individualized treatment approaches [59].
3. Advances in targeted and hormonal therapies: Targeted therapies continue to evolve, with lenvatinib approved for pMMR tumors, and active research into PI3K/AKT/mTOR inhibitors, PARP inhibitors, WEE1 inhibitors, and hormonal modulators. ER-negativity in NSMP tumors is associated with worse prognosis and reduced response to hormone therapy, prompting interest in combination endocrine strategies and newer hormonal agents [61].
4. Artificial intelligence and digital pathology: AI is transforming EC management through image-based prognostic modeling, risk prediction, and automated histologic-molecular integration [84]. These innovations aim to standardize diagnostics and support equitable access, especially in low-resource settings.
5. Fertility-preserving innovations: For selected young patients, molecular profiling supports safe fertility-sparing approaches. Hormonal therapy combined with LNG-IUS or hysteroscopic resection is used in early-stage, low-risk tumors [85]. However, caution is advised in NSMP patients with L1CAM expression or ER loss, as these features predict higher recurrence and may warrant definitive surgery [86].
6. Promoting global health equity: Efforts to expand equitable care include implementing cost-effective molecular testing algorithms, starting with MMR IHC, and integrating digital solutions like AI-based diagnostics should be the way forward [87].

A multidisciplinary, research-driven approach will be essential to overcome these barriers and deliver personalized, equitable, and effective care for all patients with endometrial cancer [88].

Molecular profiling is also shaping the selection of patients for fertility-preserving treatments, helping to safely expand conservative options for younger women. The ongoing RAINBO POLEmut-BLUE trial is evaluating adjuvant therapy omission or reduction in POLE-mutated ECs and is expected to provide crucial evidence on which molecular subtypes justify such an approach [34].

## 10. Conclusion

EC is undergoing a major shift in diagnosis and management, driven by the integration of molecular classification. This transition from traditional histologic evaluation to molecular-based diagnosis enables more accurate risk stratification and guides personalized treatment decisions. For pathologists, incorporating molecular markers into routine diagnostic practice is now essential, as these findings increasingly determine prognosis and influence the therapeutic direction.

Key alterations such as POLE mutations support treatment de-escalation due to excellent outcomes, whereas CTNNB1 mutations within the NSMP subgroup signal higher recurrence risk, even in low-grade tumors, warranting closer surveillance. MMR d, when accurately diagnosed, has direct implications for systemic therapy selection, particularly the use of immunotherapy combinations like pembrolizumab and lenvatinib.

As molecular tools become routine, pathologists must remain deeply involved—ensuring diagnostic accuracy that not only informs immediate clinical decisions but also aligns with evolving standards of individualized, research-driven care.

## Abbreviations

|             |                                                                                                                                    |
|-------------|------------------------------------------------------------------------------------------------------------------------------------|
| abn         | abnormality                                                                                                                        |
| AI          | artificial intelligence                                                                                                            |
| AMACR       | $\alpha$ -methylacyl-CoA racemase                                                                                                  |
| ARID1A      | AT-rich interactive domain- containing protein 1A                                                                                  |
| BMI         | body mass index                                                                                                                    |
| BRCA        | BReast CAncer gene                                                                                                                 |
| CCC         | clear cell carcinoma                                                                                                               |
| cDNA        | complementary DNA                                                                                                                  |
| CK          | cytokeratins                                                                                                                       |
| CNH         | copy number high                                                                                                                   |
| CT          | chemotherapy                                                                                                                       |
| CTNNB1      | catenin beta 1                                                                                                                     |
| D & C       | dilation and curettage                                                                                                             |
| D/D         | differential diagnosis                                                                                                             |
| DDC         | dedifferentiated carcinoma                                                                                                         |
| ddPCR       | droplet digital polymerase chain reaction                                                                                          |
| DUO-E trial | durvalumab with or without olaparib as maintenance therapy after first-line treatment of advanced and recurrent endometrial cancer |
| EBRT        | external beam radiation therapy                                                                                                    |
| EC          | endometrial carcinoma                                                                                                              |
| EDM         | exonuclease domain mutations                                                                                                       |
| EEC         | endometrioid endometrial carcinoma                                                                                                 |

|                |                                                               |
|----------------|---------------------------------------------------------------|
| EMA            | epithelial membrane antigen                                   |
| EPCAM          | epithelial cell adhesion molecule                             |
| ERBB2/ HER2    | human epidermal growth factor receptor 2                      |
| ER             | estrogen receptor                                             |
| ESGO           | European Society of Gynecological Oncology                    |
| ESTRO          | European Society for Radiotherapy and Oncology                |
| ESP            | European Society of Pathology                                 |
| ESMO           | European Society for Medical Oncology                         |
| ET             | Endocrine therapy                                             |
| FBXW7          | F-box and WD repeat domain-containing 7                       |
| FIGO           | International Federation of Gynecology and Obstetrics         |
| G1             | Grade 1                                                       |
| G3             | Grade 3                                                       |
| H & E          | hematoxylin and eosin                                         |
| HGSC           | high-grade serous carcinoma                                   |
| HNF1 $\beta$ + | hepatocyte nuclear factor-1 beta                              |
| HPV            | human Papilloma Virus                                         |
| HR +           | hormone receptor positive                                     |
| HRT            | hormone replacement therapy                                   |
| HT             | hormonal therapy                                              |
| ICB            | immune checkpoint blockade                                    |
| ICI            | immune checkpoint inhibitors                                  |
| IHC            | immunohistochemistry                                          |
| ISGyP          | International Society of Gynecological Pathologists           |
| KRAS           | Kirsten rat sarcoma virus                                     |
| LN             | lymph node                                                    |
| LNG-IUS        | levonorgestrel-releasing intra-uterine system                 |
| LS             | Lynch syndrome                                                |
| LVSI           | lymphovascular space invasion                                 |
| L1CAM          | L1 cell adhesion molecule                                     |
| MDT            | multidisciplinary team                                        |
| MELF           | microcystic, elongated, and fragmented pattern of myoinvasion |
| MLH1           | MutL protein homolog 1                                        |
| MMR            | mismatch repair                                               |
| MMRd           | mismatch repair deficient                                     |
| MoLIInEC       | molecularly informed endometrial cancer care                  |
| MRI            | magnetic resonance imaging                                    |
| MSH2           | MutS homolog 2                                                |
| MSH6           | MutS homolog 6                                                |
| MSI            | microsatellite instability                                    |
| MSI-H          | MSI-high                                                      |
| MSI-L          | MSI-low                                                       |
| MSS            | microsatellite stable                                         |
| mut            | mutations                                                     |
| NCCN           | National Comprehensive Cancer Network                         |
| NGS            | next-generation sequencing                                    |
| NOS            | not otherwise specified                                       |
| NSMP           | no specific molecular profile                                 |
| PARP           | poly (ADP-ribose) polymerase                                  |
| PAX8           | paired box gene 8                                             |

|                |                                                                               |
|----------------|-------------------------------------------------------------------------------|
| PCOS           | polycystic ovary syndrome                                                     |
| PCR            | polymerase chain reaction                                                     |
| PD-L1          | programmed death-ligand 1                                                     |
| PET-CT         | positron emission tomography-computed tomography                              |
| PFS            | progression-free survival                                                     |
| PIK3CA         | phosphatidylinositol 3-kinase (p110 $\alpha$ catalytic subunit)               |
| PM             | post-menopausal                                                               |
| PMB            | post-menopausal bleeding                                                      |
| pMMR           | proficient mismatch repair                                                    |
| PMS2           | postmeiotic segregation increased 2                                           |
| Pol $\delta$   | DNA polymerase delta                                                          |
| Pol $\epsilon$ | DNA polymerase epsilon                                                        |
| PORTEC-4a      | post-operative radiation therapy in endometrial carcinoma-trial 4a            |
| PPP2R1A        | protein phosphatase 2 regulatory subunit A alpha                              |
| PR             | progesterone receptor                                                         |
| ProMisE        | proactive molecular risk classifier for endometrial cancer                    |
| PTEN           | phosphatase and tensin homolog                                                |
| RAINBO trial   | refining adjuvant treatment IN endometrial cancer based on molecular features |
| RT             | radiotherapy                                                                  |
| SC             | serous carcinoma                                                              |
| SEE-FIM        | sectioning and extensively examining the FIMbriated end                       |
| SGO            | Society of Gynecologic Oncology                                               |
| SITC           | Society for Immunotherapy of Cancer                                           |
| SPOP           | speckle-type POZ protein                                                      |
| SWI/SNF        | SWItch/sucrose non-fermentable complex                                        |
| TAPER trial    | tailored adjuvant therapy in p53-wildtype/NSMP early-stage endometrial cancer |
| TCGA           | the cancer genome atlas                                                       |
| TH-BSO         | total hysterectomy with bilateral salpingo-oophorectomy                       |
| TILs           | tumor infiltrating lymphocytes                                                |
| TLS            | tertiary lymphoid structures                                                  |
| TMB            | tumor mutational burden                                                       |
| TP53           | tumor protein p53                                                             |
| TransPORTEC    | translational research consortium associated with the PORTEC-3 trial          |
| TVUS           | transvaginal ultrasound                                                       |
| UDC            | undifferentiated carcinoma                                                    |
| VTE            | venous thromboembolic events                                                  |
| VUS            | variants of uncertain significance                                            |
| WEE1           | serine/threonine protein kinase                                               |
| WHO            | World Health Organisation                                                     |
| WT1            | Wilms' tumor 1                                                                |

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# Endometrial Cancer – Prognostic Models and Risk Assessment

*Vladimír Kraus*

### Abstract

Endometrial cancer is a heterogeneous disease with outcomes influenced by a range of clinicopathological and molecular factors. Identifying reliable prognostic markers and developing robust predictive models are critical for individualized patient management. This chapter examines the role of established and emerging prognostic markers, including tumor grade, lymphovascular space invasion, and molecular alterations, in stratifying patients by risk. Additionally, it discusses the development of prognostic models that integrate these markers with clinical variables to predict outcomes such as recurrence risk and survival. Special emphasis is placed on the utility of nomograms—graphical prediction tools that offer personalized risk assessments and guide clinical decision-making. The integration of these tools into clinical practice promises to enhance the precision of endometrial cancer management, optimizing treatment strategies and improving patient outcomes.

**Keywords:** prognosis, prognostic model, nomogram, risk stratification, biomarkers, recurrence, endometrial cancer

### 1. Introduction

Endometrial cancer (EC) has recently attracted significant attention within the medical and research communities, owing to its increasing incidence and complex biological mechanisms. As the most prevalent gynecologic malignancy in developed nations, EC is a major contributor to cancer-related morbidity and mortality on a global scale. Although many cases are identified at an early stage due to characteristic symptoms such as abnormal uterine bleeding, advanced-stage disease continues to pose substantial therapeutic challenges. The aging population and the rising prevalence of obesity—two primary risk factors for EC—further emphasize the need for a deeper understanding and more effective management of this malignancy [1, 2].

The global incidence of EC is steadily rising, largely as a consequence of the obesity epidemic. Obesity induces a pro-inflammatory state that promotes estrogen-driven carcinogenesis, particularly in the more common endometrioid subtype. Increasingly, younger women are affected by obesity and its associated conditions, such as insulin resistance and chronic inflammation, which further elevate the risk of EC. Additionally, polycystic ovary syndrome, characterized by chronic anovulation and hyperandrogenism, is a notable risk factor among younger women. The absence of ovulation leads to prolonged, unopposed estrogen exposure, devoid of the

counter-regulatory effects of progesterone, thereby creating an environment conducive to endometrial hyperplasia and eventual malignancy [3].

EC is not a homogenous disease; rather, it comprises a spectrum of histological subtypes, each with distinct molecular features and clinical behaviors. Recent advancements in molecular profiling have illuminated the heterogeneity of EC, uncovering unique pathways of tumorigenesis and mechanisms of therapeutic resistance. This complexity necessitates a more sophisticated and individualized approach to treatment strategies [4].

Historically, the management of EC has been grounded in a combination of surgical intervention, radiation therapy, and chemotherapy, often applied using a generalized treatment approach. However, the limitations of this strategy are increasingly evident. While early-stage, low-grade endometrioid carcinomas often respond well to surgical management, high-risk subtypes, such as serous and clear cell carcinomas, frequently demonstrate resistance to standard therapies and are associated with poor prognoses. These challenges have driven a paradigm shift toward precision medicine, aiming to personalize treatment strategies based on the molecular characteristics of individual tumors [5].

Traditional prognostic indicators, such as tumor grade, stage, and lymphovascular space invasion, are now complemented by molecular markers, including TP53 mutations, PTEN alterations, and disruptions in the PI3K/AKT pathway. These molecular features have been incorporated into advanced classification systems, such as the system based on findings from The Cancer Genome Atlas (TCGA), which categorizes EC into four molecular subgroups with distinct prognostic implications. A surrogate molecular classification system further divides tumors into POLE ultramutated (POLEmut), mismatch repair deficient (MMRd), p53 abnormal (p53abn), and no specific molecular profile (NSMP), providing a nuanced framework for individualized treatment planning [6, 7].

Recent advancements in EC classification have shifted the paradigm from a system predominantly based on anatomical and histopathological features to one that integrates molecular characteristics for more precise risk stratification and treatment planning. The most notable development is the incorporation of molecular subtypes into the staging framework. This represents a significant evolution from the 2009 FIGO staging system, which primarily relied on the anatomical extent of disease. The 2023 FIGO system now includes molecular classification (when available) to enhance the accuracy of staging and prognostic assessment. Although molecular classification is not mandatory in the updated FIGO system, its application is strongly recommended, particularly for high-grade endometrioid cancers, where it plays a pivotal role in refining risk stratification and informing therapeutic decisions [8].

In parallel, machine learning and artificial intelligence are increasingly being utilized to advance prognostic modeling. These technologies can synthesize complex datasets encompassing clinical, histological, and molecular variables to achieve more accurate outcome predictions. Such innovations hold the potential to improve individualized patient care while optimizing the allocation of healthcare resources [9].

For younger women, predictive tools are especially critical in balancing recurrence risk with future fertility considerations. These tools inform decisions regarding the intensity of follow-up and the timing of reproductive planning. For instance, high-risk patients may require expedited childbearing plans or additional adjuvant hormonal therapies to mitigate recurrence risks. Conversely, patients stratified as low-risk can pursue conservative management with greater confidence in its safety and efficacy [3, 5].

## 2. FIGO 2023 classification

The 2023 FIGO staging system acknowledges that EC is not a singular disease entity but a heterogeneous group of malignancies characterized by distinct molecular drivers, which significantly influence prognosis and therapeutic responses. While the extent of tumor spread remains a fundamental prognostic factor, the FIGO stage is determined based on the anatomical dissemination of the tumor, including the depth of myometrial invasion and the involvement of regional lymph nodes.

In 2013, TCGA conducted an integrated molecular characterization of EC, identifying four prognostically significant subgroups based on mutational burden and somatic copy-number variations [10]. Subsequent research has demonstrated that more accessible and cost-effective immunohistochemical and molecular tests can effectively serve as surrogates for the complex and expensive analyses performed by TCGA [11]. The 2023 FIGO staging system incorporates this molecular classification, marking a significant advancement in the understanding and management of EC. This integration enhances prognostic precision and facilitates the identification of treatment-relevant subgroups of patients. To reflect the molecular subtype, the 2023 FIGO system allows the addition of an “m” to the standard stage when molecular data is available [12]. This molecular-based classification system delineates four distinct subtypes of EC. Studies consistently demonstrate that the 2023 FIGO system provides superior predictive accuracy for progression-free survival (PFS) and overall survival (OS), underscoring its clinical utility in tailoring treatment strategies and improving patient outcomes [6]. The four distinct molecular patterns recognized within EC, including their prognostic outlook, are summarized in **Table 1** [5, 7, 13].

Two molecular subtypes of EC hold particular clinical significance in early-stage disease (stage I–II) due to their distinct prognostic and therapeutic implications. The POLEmut subtype is typically associated with low-grade endometrioid EC, but tumors with this mutation demonstrate an excellent prognosis irrespective of histological grade, stage, or other clinicopathological factors. In early-stage disease, the presence of a pathogenic POLE mutation results in downstaging, with

| Molecular class                                                          | Description                                                                                                                                                                                                                                                                |
|--------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| POLE-mutated<br>TCGA group: ultramutated                                 | Defined by a high frequency of somatic pathogenic mutations within the exonuclease domain of the POLE gene, responsible for encoding DNA polymerase epsilon.<br><i>Prognosis:</i> very favorable prognosis, with a low risk of relapse.                                    |
| mismatch repair deficient<br>TCGA group: microsatellite instability high | Defined by defects in mismatch repair (MMR) genes, such as MLH1, MSH2, MSH6, and PMS2, resulting in microsatellite instability.<br><i>Prognosis:</i> varies, based on clinicopathological features.                                                                        |
| p53-abnormal<br>TCGA group: copy-number high                             | Characterized by TP53 mutations and frequently associated with serous or high-grade endometrioid histological subtypes.<br><i>Prognosis:</i> poor prognosis, even in early-stage disease, due to aggressive tumor behavior and higher recurrence rates.                    |
| no specific molecular profile<br>TCGA group: copy-number low             | Lacks specific molecular alterations, including POLE mutations, MMR defects, or p53 abnormalities, and is often associated with estrogen receptor-positive endometrioid cancers.<br><i>Prognosis:</i> intermediate prognosis, poor if they are estrogen receptor-negative. |

**Table 1.**  
*Four distinct molecular subtypes of EC, with prognostic outlook.*

uterus-confined EC classified as stage IAmPOLEmut. This subtype's exceptionally favorable prognosis suggests that patients may not require adjuvant therapy, even in cases with other high-risk features [14, 15].

In contrast, tumors with a p53abn are associated with poor outcomes, even in early-stage EC. When these abnormalities are identified in uterus-confined tumors with myometrial invasion, the disease is upstaged to stage IICmp53abn. This upstaging reflects the aggressive nature of p53-abnormal tumors, which may benefit from the addition of chemotherapy to their treatment regimen. Furthermore, the negative impact of p53abn on prognosis extends to advanced stages of disease [16, 17].

The 2023 FIGO staging system integrates molecular subtypes as critical prognostic factors, particularly in early-stage EC. By combining molecular information with anatomical and histopathological data, the system allows for a more precise and personalized assessment of patient risk, facilitating better-informed treatment decisions. Although the incorporation of molecular classification is currently encouraged, it is not yet mandatory [6]. Interestingly, a small subset of tumors exhibits features of more than one molecular subtype, known as multiple-classifier EC, which further underscores the complexity and heterogeneity of the disease [18].

### **3. Prognostic models**

In cancer research and clinical practice, prognostic models are mathematical or statistical tools designed to predict the probable outcomes or progression of a disease for individual patients. These models integrate a wide range of factors, including clinical, pathological, and molecular data, to estimate key outcomes such as OS, PFS, disease-free survival (DFS), or the risk of recurrence [19].

#### **3.1 Clinical models**

The systemic immune-inflammation index (SII) is a biomarker reflecting the interplay between immune function and inflammation, providing insights into the body's comprehensive immune status. It is calculated using the formula  $SII = (\text{neutrophil count} \times \text{platelet count}) / \text{lymphocyte count}$ . A decrease in SII indicates lower neutrophil and platelet counts alongside higher lymphocyte counts, suggesting a more favorable immune condition. Conversely, elevated SII values reflect a pro-inflammatory microenvironment that fosters tumor progression. High neutrophil and platelet counts are markers of systemic inflammation, while low lymphocyte counts point to diminished anti-tumor immunity. Chronic inflammation contributes to genetic instability, angiogenesis, and tumor proliferation, correlating with poor clinical outcomes, higher recurrence rates, and therapy resistance [20, 21].

In the context of EC, an elevated SII score has been shown to significantly predict worse OS and PFS [22]. The SII is an effective tool for forecasting both short- and long-term prognoses in EC patients. Recent studies have incorporated SII into clinical prognostic models alongside FIGO staging and lymph node status. Notably, comparisons of preoperative and postoperative SII values highlight postoperative SII as a significant, independent prognostic factor. A cutoff value of  $2.93 \times 10^{12}$  for postoperative SII was identified, with patients in the high SII group exhibiting significantly worse OS and increased tumor progression compared to those with lower SII values [23]. A diagram of SII is illustrated in **Figure 1**.



**Figure 1.**  
Diagram of the systemic immune-inflammation index.

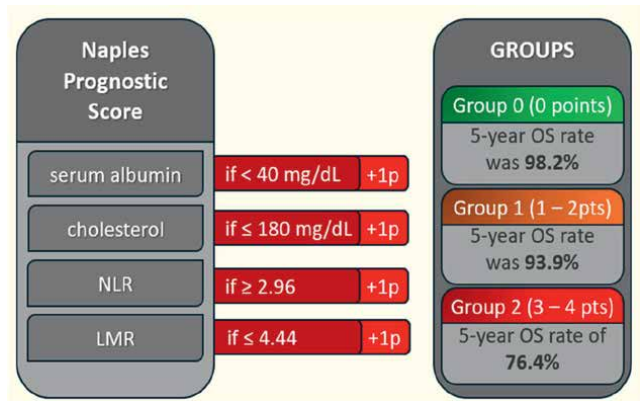
In addition to systemic markers, localized immunological changes within the tumor microenvironment (TME) play a critical role in the development and progression of EC. Immune cell infiltration and its modulation within the TME significantly influence prognosis. Li and Wan proposed a classification of EC based on immune cell infiltration profiles, leveraging gene expression data, immune cell profiles, and immunomodulator expression from the Uterine Corpus Endometrial Carcinoma cohort of TCGA ( $n = 538$ ). This classification offers valuable insights into the immunological landscape of EC and its prognostic implications, as summarized in **Table 2** [24].

The monocyte-lymphocyte ratio (MLR) serves as a prognostic marker in oncology, including EC, by reflecting the balance between the pro-tumor activity of monocytes and the anti-tumor activity of lymphocytes. Elevated MLR values have been associated with poor clinical outcomes, particularly in stage I endometrioid EC, where higher MLR values correlate with significantly increased recurrence rates. While the cutoff values for MLR vary across studies depending on the patient population and methodology, an average cutoff value of 0.2 has been commonly reported in the literature [25, 26]. Similarly, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) have been linked to prognosis in EC. Elevated levels of these ratios are generally associated with poorer outcomes, although studies suggest that NLR and PLR may not function as independent prognostic factors in EC [26].

The Naples Prognostic Score (NPS) offers a comprehensive assessment of a patient's inflammatory and nutritional status, making it a valuable tool in predicting cancer prognosis and incidence. The NPS integrates four readily available parameters: serum

| Subtype                          | Description                                                                                                                                                                                                                                                       | Prognosis                                           |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| C1 (immunodepression)            | This subtype is defined by a predominant wound-healing and IFN- $\gamma$ signature, characterized by the lowest Th1:Th2 ratio and minimal expression of PD-1 and PD-L1. Notably, C1 demonstrates the weakest immunologic activity.                                | overall worst prognosis and highest metastatic rate |
| C2 (IFN- $\gamma$ dominant type) | This subtype is characterized by elevated levels of IFN- $\gamma$ , lymphocytes, and macrophages.                                                                                                                                                                 | less favorable outcomes                             |
| C3 (inflammatory type)           | This subtype is marked by extensive lymphocyte and macrophage infiltration, minimal wound-healing, and the highest PD-1 expression. It exhibits elevated levels of Th17 and Treg cells, the highest Th1/Th2 cell ratio, and the most robust immunologic activity. | best prognosis                                      |
| C4 (balanced type)               | This subtype demonstrates a relatively balanced immune cell distribution and a well-balanced activation of immune pathways.                                                                                                                                       | less favorable outcomes                             |

**Table 2.**  
Immunological subtypes of endometrial cancer.



**Figure 2.**  
*Diagram of the Naples Prognostic Score.*

albumin, total cholesterol, NLR, and lymphocyte-to-monocyte ratio (LMR). Each parameter is scored as 0 or 1 based on specific cutoff thresholds, and the total score categorizes patients into three prognostic groups, as is illustrated in **Figure 2** [27].

Higher NPS values are associated with an increased incidence of cancer in the general population and poorer outcomes across various malignancies. NPS has been established as an independent prognostic factor in multiple cancer types, including colorectal, endometrial, pancreatic, and non-small cell lung cancer [27, 28]. In the context of EC, elevated NPS scores correlate with worse PFS and OS. One study demonstrated a significant decline in 1- to 5-year OS rates among EC patients as NPS scores increased. Patients in NPS group 1 had a 1- to 5-year OS rate of 98.2%, compared to 76.4% in those in group 2 [29]. Scoring parameters and NPS groups are summarized in **Table 3**.

The Endometrial Cancer Individualized Scoring System (ECISS) is a machine learning-based prognostic model designed to provide personalized risk assessments and predict outcomes for women with EC. This model integrates patient demographics, disease characteristics, and treatment plans to offer precise prognostic insights and tailor decision-making. Developed through a retrospective, multi-center study that included data from 1150 patients across nine European gynecologic cancer centers (2008–2015), ECISS comprises three predictive models aimed at estimating cancer-specific survival (CSS) and DFS at 3 and 5 years.

| Parameter                      | 0 points    | 1 point     |
|--------------------------------|-------------|-------------|
| Serum albumin                  | ≥ 40 mg/dL  | < 40 mg/dL  |
| Total cholesterol              | > 180 mg/dL | ≤ 180 mg/dL |
| Neutrophil to lymphocyte ratio | < 2.96      | ≥ 2.96      |
| Lymphocyte-to-monocyte ratio   | > 4.44      | ≤ 4.44      |
| NPS Groups                     | Group 0     | 0 points    |
|                                | Group 1     | 1–2 points  |
|                                | Group 2     | 3–4 points  |

**Table 3.**  
*Naples Prognostic Scoring system.*

- Model I (preoperative model) focuses on patient demographics and preoperative disease characteristics, offering an initial survival probability at the time of diagnosis. Notably, FIGO staging is not included in this model, as it aims to provide a preoperative risk assessment.
- Model II (management model) builds upon the survival probability derived from Model I by incorporating treatment details, such as surgery, radiotherapy, and chemotherapy. This model predicts outcomes based on the selected treatment plan, allowing clinicians to evaluate the impact of various management strategies.
- Model III (postoperative model) refines survival probabilities further by integrating postsurgical information, including residual disease and treatment-related complications. This model provides the most comprehensive and accurate prognostic assessment.

The study demonstrated that the ECISS models predict 5-year CSS with high accuracy, with Model III achieving the best performance (87.35% for the training set and 86.05% for the testing set). The models also accurately predicted 3-year CSS and both 3- and 5-year DFS. Importantly, the ECISS models outperformed the 2009 FIGO staging system in diagnostic accuracy, highlighting their potential as superior tools for individualized risk assessment and clinical decision-making in EC management [30].

HECTOR (Histopathology-Based Endometrial Cancer Tailored Outcome Risk) is a multimodal deep learning prognostic model specifically developed to predict the risk of distant recurrence in patients with EC. This advanced model utilizes hematoxylin and eosin (H&E)-stained whole-slide images and tumor stage (based on the 2009 FIGO classification) as input data. By combining histopathological and anatomical information, HECTOR offers an innovative approach to individualized prognostic assessment. The model was developed and tested using data from 2072 patients across eight EC cohorts, including participants from the PORTEC-1, -2, and -3 randomized trials. Additionally, data from the TCGA Uterine Corpus Endometrial Carcinoma cohort were utilized for self-supervised learning. The development process followed a two-step approach. The first step involved extracting features from H&E-stained tumor images using deep learning techniques. In the second step, these image-based features were combined with molecular classification derived from the images and surgically assessed anatomical stage to predict the risk of distant recurrence. HECTOR generated a continuous risk score for each patient, representing their predicted probability of distant recurrence. Based on this score, patients were stratified into three risk categories: low-risk, intermediate-risk, and high-risk. These groups demonstrated significantly different clinical outcomes, with 10-year distant recurrence-free probabilities of 97.0% for the low-risk group, 77.7% for the intermediate-risk group, and 58.1% for the high-risk group [31].

### **3.2 Molecular models**

The PROMISE study (Proactive Molecular Risk Classifier for Endometrial Cancer) represents a groundbreaking effort to incorporate molecular classifications into the clinical management of endometrial tumors [32]. Launched in 2015 and validated through subsequent studies, including a key retrospective validation trial published in

2018, the PROMISE study was instrumental in shaping the molecular framework that underpins the 2023 FIGO classification of EC [11, 33].

The primary aim of the PROMISE study was to refine risk stratification and treatment decision-making by leveraging molecular features of endometrial tumors. To create a clinically applicable alternative to complex genomic classifications, the study introduced the PROMISE molecular classification system, which categorizes EC into four distinct prognostic subgroups based on specific molecular markers. Unlike traditional methods relying on histotype and tumor grade, PROMISE provided a more robust and objective approach by focusing on the presence or absence of specific proteins or mutations. The four subtypes identified are POLEmut, MMRd, p53abn, and p53 wild-type (p53wt). The PROMISE system improved on traditional histopathological approaches by effectively distinguishing between high-grade tumors with contrasting prognoses. For example, it can differentiate between POLE-mutated tumors with excellent outcomes and p53-abnormal tumors with poor outcomes, a distinction that is not possible with conventional histotype and grade assessments. By incorporating molecular data into the diagnostic and prognostic process, the PROMISE system has set a new standard for EC risk stratification, ensuring more precise treatment planning and identifying patients who may benefit from additional interventions, such as genetic counseling for Lynch syndrome [34]. **Table 4** holds a summary of the four classes.

A study by Zagidullin et al. [35] expanded on the foundational work of the PROMISE study by incorporating an extended set of clinical variables and biomarkers to refine prognostic modeling for EC. The research added clinical parameters such as age, FIGO stage, histological subgroup, deep myometrial invasion, lymphovascular invasion, and tumor diameter > 3 cm, along with additional biomarkers, including tumor diameter > 5 cm, peritoneal washing status, estrogen receptor (ER) status, and CD171 expression. Two prognostic algorithms were trained on a dataset of 842 patients to model disease-specific survival: the Cox proportional hazards regression and the optimal survival tree models. The latter model demonstrated significant

| Molecular class           | Description                                                                                                                                                                                                                                                                                                                                               | Prognosis                |
|---------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| POLE-mutated              | These tumors are frequently observed in younger women with lower BMIs and exhibit unexpectedly aggressive pathological characteristics.                                                                                                                                                                                                                   | very favorable prognosis |
| Mismatch repair deficient | MMRd tumors may exhibit aggressive features, including myometrial invasion and lymphovascular space invasion. This subtype is also associated with Lynch syndrome, warranting referral of affected patients for genetic counseling and testing.                                                                                                           | intermediate prognosis   |
| p53 wild-type             | Tumors in this group lack mutations in the POLE gene and exhibit a wild-type p53 protein expression pattern. Unlike p53abn tumors, 1–80% of tumor cell nuclei display heterogeneous staining.                                                                                                                                                             | intermediate prognosis   |
| p53 abnormal              | This subtype comprises tumors harboring either null or missense mutations in the p53 protein, identified by aberrant p53 immunohistochemical staining. These tumors are commonly observed in older women and are associated with non-endometrioid histotypes, advanced stages, an elevated risk of recurrence or progression, and reduced survival rates. | poor prognosis           |

**Table 4.**  
*Four molecular classes of EC with their prognostic outlook.*

improvements in prognostic accuracy, particularly within the MMRd and p53abn PROMISE subgroups. The inclusion of biomarker data led to substantial increases in the C-index for these groups, with the largest gains being 10.8% in the MMRd group and 8.7% in the p53abn group. Among the newly integrated biomarkers, CD171 emerged as a critical prognostic factor, particularly in the p53abn group. The optimal survival tree model identified CD171 status as the most informative variable for stratifying the cohort and predicting survival, with its expression strongly associated with poor outcomes [35].

The PORTEC (Post-Operative Radiation Therapy in Endometrial Cancer) studies are a landmark series of clinical trials that have significantly advanced the management of EC. These trials have played a pivotal role in shaping current clinical practices by evaluating the efficacy and safety of postoperative radiation therapy. The ongoing fourth phase of the PORTEC trials focuses on comparing individualized adjuvant treatment based on molecular-integrated risk profiles with standard adjuvant therapies for women with high-intermediate risk EC, marking a shift toward personalized treatment approaches [36, 37].

The TransPORTEC studies build upon the foundation of the PORTEC trials by conducting translational research to understand the biological mechanisms underlying clinical outcomes. Utilizing biobank samples and data from the PORTEC trials, TransPORTEC has conducted extensive molecular and immunological analyses. These studies validated a simple molecular classification system for EC, with four key prognostic subgroups: POLEmut, MMRd, p53abn, and NSMP. TransPORTEC also developed a cost-effective and clinically feasible method for molecular classification by employing targeted sequencing and immunohistochemistry on formalin-fixed paraffin-embedded tumor samples [38].

### 3.3 Genetic models

TCGA is a landmark initiative launched in 2005 as a collaborative effort between the National Cancer Institute and the National Human Genome Research Institute. Its primary objective is to systematically catalog the genetic mutations, epigenetic changes, and molecular alterations that drive various cancers. By characterizing over 11,000 tumor samples from 33 cancer types, including EC, TCGA has revolutionized cancer research by providing multi-omics data, encompassing whole-exome and whole-genome sequencing, RNA sequencing (mRNA, miRNA, and lncRNA), DNA methylation, chromatin accessibility, and protein expression with post-translational modifications [39].

Thanks to TCGA, EC was classified into four distinct molecular subtypes and eventually led to new FIGO classification, as was mentioned earlier. Its prognostic value was soon discovered, and genes associated with EC prognosis, copy-number variations, methylation patterns, and differentially expressed genes were studied [40]. Using TCGA data, researchers have constructed protein-protein interaction (PPI) networks to study the functional connectivity of differentially expressed genes. These analyses identified “hub genes” that exhibit high connectivity within PPI networks and are pivotal in the development and progression of EC [41, 42]. One recent study, leveraging data from the Gene Expression Omnibus (GEO) database, identified 304 differentially expressed genes, of which 78 were hub genes. Among these, three genes—ENG, GNG4, and ECT2—were validated as potential biomarkers for EC using gene expression profiling interactive analysis. ENG and GNG4 were found to act as tumor suppressors, while ECT2 was identified as an oncogene due to its significant dysregulation in tumor samples compared to normal tissues [43]. Among the genes

linked to EC prognosis, UBE2C (Ubiquitin-Conjugating Enzyme E2 C) has emerged as particularly noteworthy. UBE2C plays a critical role in cell cycle progression by regulating the anaphase-promoting complex/cyclosome, ensuring the orderly degradation of cell cycle regulators. Overexpression of UBE2C disrupts normal mitosis, leading to resistance to cell cycle checkpoints and contributing to tumorigenesis. Its strong association with poor prognosis highlights its potential as a key biomarker and therapeutic target in EC [40, 44, 45]. **Table 5** offers an overview of recent genetic prognostic models.

When discussing genetics in the context of cancer, microRNAs (miRNAs) are indispensable due to their regulatory functions in gene expression and their significant roles in pathways critical to tumor progression. miRNAs act as post-transcriptional regulators by modulating the expression of oncogenes or tumor suppressor genes, thereby influencing key cellular processes such as proliferation, apoptosis, invasion, metastasis, and therapy resistance. Their dual roles as either oncogenic or tumor-suppressive miRNAs further underscore their relevance in cancer biology. One of the most compelling features of miRNAs is their stability in both tissues and biofluids, such as blood, urine, and saliva, which makes them highly suitable as non-invasive biomarkers for cancer prognosis. In EC, specific miRNAs have been linked to various prognostic factors, including tumor grade, stage, and patient outcomes, highlighting their potential as valuable tools for early detection, risk stratification, and monitoring treatment responses [52]. **Table 6** offers an overview of current miRNA-based prognostic models.

| Study                        | Description                                                                                                                                                                                                                                                                                              | Results                                                                                           |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Huang et al. [46]<br>n = 587 | <ul style="list-style-type: none"><li>• 4 hub genes (BUB1B, NDC80, TPX2, TTK)</li><li>• additional parameters: age, stage, grade</li></ul>                                                                                                                                                               | 2-year OS (AUC 0.807)<br>3-year OS (AUC 0.783)<br>5-year OS (AUC 0.786)                           |
| Li et al. [47]<br>n = 381    | <ul style="list-style-type: none"><li>• 11 autophagy-related genes (BID, CAPN2, CDKN2A, DLC1, GRID2, IFNG, MYC, NRG3, P4HB, PTK6, TP73)</li><li>• additional parameters: age, stage, grade</li></ul>                                                                                                     | 1-year OS (AUC 0.733)<br>3-year OS (AUC 0.795)<br>5-year OS (AUC 0.823)                           |
| Wu et al. [48]<br>n = 567    | <ul style="list-style-type: none"><li>• 11 lymph node metastasis-related genes (C14orf28, HNRNPA3P1, DSP, ACACB, TPX2, HMGB3, ATP8B4, PPP1R14C, CIRBP, CDC6, DTWD1)</li><li>• additional parameters: age, stage, grade, peritoneal cytology</li></ul>                                                    | 1-year OS (AUC 0.669)<br>3-year OS (AUC 0.702)<br>5-year OS (AUC 0.718)                           |
| Wang et al. [49]<br>n = 541  | <ul style="list-style-type: none"><li>• 13 inflammatory response-related genes (GABBR1, LAMP3, LCK, LPAR1, MEP1A, MXD1, NDP, P2RX4, P2RY2, PSEN1, ROS1, SLC11A2, TNFSF10)</li><li>• additional parameters: age, grade, stage</li></ul>                                                                   | 1-year OS (AUC 0.778)<br>3-year OS (AUC 0.793)<br>5-year OS (AUC 0.814)                           |
| Yu et al. [50]<br>n = 542    | <ul style="list-style-type: none"><li>• 4 EMT related genes (SIRT2, SIX1, CDKN2A, PGR)</li><li>• additional parameters: age, grade, stage</li></ul>                                                                                                                                                      | 1-year OS (AUC 0.708)<br>3-year OS (AUC 0.743)<br>5-year OS (AUC 0.793)<br>10-year OS (AUC 0.744) |
| Wang et al. [51]<br>n = 575  | <ul style="list-style-type: none"><li>• 22 ubiquitination-related genes (UBE2S, UBE2D2, TOM1, RNF114, RNF122, MDM2, PIAS4, NHLRC1, TRIM46, MAR CH11, TRIM9, ANAPC4, TRAF1, KLHL40, TNFAIP1, ANAPC2, CIAO1, WDR82, ASB9, ASB2, FBXO40, EBF2)</li><li>• additional parameters: age, grade, stage</li></ul> | 3-year OS (AUC 0.722)<br>5-year OS (AUC 0.786)                                                    |

**Table 5.**  
*An overview of prognostic models for EC, based on genetic profiling.*

| Study                                                                                                                                                       | Description                                                                                                                                                                                                                                                                   | Results                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|
| Wang et al. [53]<br>n = 860                                                                                                                                 | 5 prognostic miRNAs identified (hsa-miR-18b-3p, hsa-miR-128-3p, hsa-miR-106a-5p, hsa-miR-455-5p, and hsa-miR-7706)<br><ul style="list-style-type: none"><li>• additional parameters: age, grade, stage</li></ul>                                                              | 3-year OS (AUC 0.751)<br>5-year OS (AUC 0.749)                          |
| Lu et al. [54]<br>n = 497                                                                                                                                   | 3 immune-related miRNAs (hsa-miR-146a-5p, hsa-miR-139-5p, and hsa-miR-1301-3p)<br><ul style="list-style-type: none"><li>• additional parameters: age, grade, stage, histological type</li></ul>                                                                               | 1-year OS (AUC 0.64)<br>3-year OS (AUC 0.637)<br>5-year OS (AUC 0.686)  |
| Huang et al. [55]<br>n = 569                                                                                                                                | 4 key miRNAs identified (miR-31-5p, miR-34a-5p, miR-26a-1-3p, and miR-4772-3p)<br><ul style="list-style-type: none"><li>• additional parameters: age, grade, stage</li></ul>                                                                                                  | 1-year OS (AUC 0.78)<br>3-year OS (AUC 0.82)<br>5-year OS (AUC 0.88)    |
| Ye et al. [56]<br>n = 579                                                                                                                                   | 7 necroptosis-associated miRNAs identified (miR-15a-5p, miR-148a-3p, miR-7-5p, miR-141-3p, miR-200a-5p, miR-223-3p, and miR-16-5p)<br><ul style="list-style-type: none"><li>• additional parameters: age, grade, stage</li></ul>                                              | 1-year OS (AUC 0.678)<br>3-year OS (AUC 0.652)<br>5-year OS (AUC 0.656) |
| Huang et al. [57]<br>n = 575<br>NOTE                                                                                                                        | identified 3636 differentially expressed mRNAs, 249 miRNAs, and 252 lncRNAs<br><ul style="list-style-type: none"><li>• a ceRNA network comprising 19 lncRNA-miRNA pairs and 434 miRNA-mRNA pairs was constructed</li><li>• additional parameters: age, grade, stage</li></ul> | 1-year OS (AUC 0.733)<br>3-year OS (AUC 0.795)<br>5-year OS (AUC 0.820) |
| This study utilized competing endogenous RNAs (ceRNA)—a class of RNA molecules that interact with and regulate each other by competing for shared microRNAs |                                                                                                                                                                                                                                                                               |                                                                         |

**Table 6.**  
*An overview of prognostic models for EC, utilizing miRNAs.*

## 4. Nomograms

Nomograms have emerged as indispensable tools in the prognostic assessment of EC, offering a more individualized prediction of outcomes compared to traditional staging systems. By incorporating multiple variables, including clinical, pathological, and molecular factors, nomograms enable nuanced risk stratification and guide personalized clinical decision-making. These tools are particularly effective for predicting outcomes such as OS, DFS, PFS, recurrence, and lymph node metastasis.

The performance of nomograms is commonly assessed using the concordance index (C-index), a statistical measure of a model's ability to differentiate between outcomes. A C-index greater than 0.7 is generally considered indicative of good predictive accuracy. Complementary metrics, such as calibration curves and decision curve analysis, are used to evaluate the agreement between predicted and observed outcomes and to quantify the clinical utility of the nomogram by assessing its net benefit in decision-making.

Nomograms also excel in their practical utility. By presenting risk calculations in a clear visual format, they simplify the communication of complex statistical predictions, facilitating discussions between clinicians and patients about prognostic risks and treatment options. For example, a nomogram may identify patients at low-risk of recurrence, suggesting that sentinel-node biopsy or adjuvant therapy might not be necessary, while pinpointing high-risk patients who could benefit from more aggressive interventions.

The reliability of nomograms, however, hinges on the quality and representativeness of the data used in their development. Poor-quality or biased data can

compromise predictive accuracy, emphasizing the need for rigorous validation and the integration of high-quality datasets. Despite these challenges, nomograms remain a cornerstone of modern oncology, bridging complex data analyses with practical, patient-centered care [58, 59].

Given the importance of survival outcomes to most patients, many nomograms are specifically designed to predict OS, DFS, or PFS. **Table 7** provides an overview of recent nomograms addressing these outcomes, including the variables considered and their predictive accuracies. These tools continue to evolve, integrating advances in molecular and clinical profiling, and play a vital role in improving the precision of EC management.

Prognostic nomograms trying to predict the presence of lymph node or distant metastasis in EC are another useful tool for the clinician, enhancing the precision of preoperative and intraoperative risk assessments. These predictive models significantly

| Study                                          | Parameters                                                                                                                                                                            | Monitored                                                              |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Li et al. [60]<br>n = 63,510                   | age, marital status, tumor size, histological type, lymph node metastasis, tumor grade, and clinical stage                                                                            | 3-year OS and CSS (C-index 0.816)<br>5-year OS and CSS (C-index 0.850) |
| Zhu et al. [61]<br>n = 63,729                  | age, race, year of diagnosis, grade, stage, tumor size                                                                                                                                | CSS (C-index 0.859)<br>OS (C-index 0.782)                              |
| Xie et al. [62]<br>n = 10,447                  | age, race, marital status, grade, histology, tumor size, FIGO stage, number of positive regional lymph nodes                                                                          | CSM (C-index 0.857)                                                    |
| Ni et al. [63]<br>n = 569                      | 12 differentially expressed miRNAs                                                                                                                                                    | 3- and 5-year OS (C-index 0.74)                                        |
| Wang et al. [64]<br>n = 1020                   | postmenopause, lymph node metastasis, lymphovascular space invasion, histological type, histological differentiation, parametrial involvement                                         | 3-year PFS (C-index 0.891)<br>5-year PFS (C-index 0.842)               |
| Wu et al. n = 1172 [65]<br>NOTE                | age, marital status, tumor size, tumor stage, lymphadenectomy, radiotherapy, chemotherapy<br>Specifically developed for low-grade endometrial stromal sarcoma                         | 5- and 10-year OS (C-index 0.814)                                      |
| Cheng et al. [66]<br>n = 2329<br>NOTE          | age, tumor size, stage, surgery, number of lymph nodes examined, lymph node metastasis, radiotherapy, chemotherapy<br>Specifically developed for uterine clear cell carcinoma         | CSS (C-index 0.778)                                                    |
| Nanthamongkolkul et al. [67]<br>n = 69<br>NOTE | Body mass index, stage, adjuvant chemotherapy<br>Specifically developed for endometrial carcinosarcoma                                                                                | 3-year OS (C-index 0.72)                                               |
| Yan et al. [68]<br>n = 1542<br>NOTE            | grade, histological type, surgery, adjuvant chemotherapy, adjuvant radiotherapy, brain metastasis, liver metastasis<br>Tailored specifically for patients with EC and lung metastasis | 1- and 3-year OS (C-index 0.75)                                        |
| Zheng et al. [69]<br>n = 2799<br>NOTE          | race, histological type, grade, metastasis status/location, surgery, lymphadenectomy, chemotherapy<br>Tailored specifically for patients with EC and distant metastasis               | 1-, 3- and 5-year OS (C-index 0.755)                                   |

**Table 7.**  
*A compilation of the most recent prognostic nomograms for EC.*

| Study                                | Parameters                                                                                                                                                                                       | Results         |
|--------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Wang et al. [70]<br>n = 1076<br>NOTE | metabolic risk score, histological type, grade, depth of myometrial invasion<br>Made specifically to predict the presence of lymphovascular space invasion                                       | AUC = 0.790     |
| Wang et al. [71]<br>n = 1517<br>NOTE | histological type, grade, depth of myometrial invasion, LVSI, cervical involvement, parametrial involvement, hemoglobin levels<br>Made specifically to predict the risk of lymph node metastasis | C-index = 0.916 |
| Zhang et al. [72]<br>n = 276<br>NOTE | depth of myometrial invasion (assessed by MRI), CA125, CA19-9, PLR<br>Made specifically to predict the risk of lymph node metastasis                                                             | C-index = 0.842 |

**Table 8.**  
*An overview of nomograms trying to predict lymph node or distant metastasis.*

| Study                                | Parameters                                                                                                                                                | Results         |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| Jiang et al. [73]<br>n = 419<br>NOTE | histological type, myometrial invasion, cervical stromal invasion, Ki67 index, ER expression, p53 expression<br>Made specifically for stage I and II EC   | C-Index = 0.832 |
| Jiang et al. [74]<br>n = 775         | inflammation-immunity-nutrition score, age, clinical stage, pathological type, myometrial invasion, LVSI, Ki67 expression, ER expression, p53 expression  | C-Index = 0.887 |
| Miao et al. [75]<br>n = 517          | age, clinical stage, postoperative CA125, positive preoperative ultrasound, chemotherapy history, cervical invasion, vascular invasion, surgical approach | C-index = 0.851 |
| Zhu et al. [76]<br>n = 289           | age-adjusted Charlson comorbidity index, peritoneal cytology, clinical stage                                                                              | C-index = 0.895 |

**Table 9.**  
*An overview of nomograms trying to assess the risk of recurrence of EC.*

influence clinical decision-making by providing individualized risk profiles that guide the extent of surgical staging and the need for adjuvant therapies **Table 8**.

The question of recurrence is significant for patients that chose fertility-sparing procedures or for the clinician considering adjuvant therapies. By identifying high-risk patients, nomograms allow for earlier and more targeted interventions, potentially preventing recurrence and improving prognosis **Table 9**.

## 5. Conclusions

Endometrial cancer represents a growing health challenge, driven by increasing incidence and diverse molecular and clinical characteristics. Advances in molecular profiling have transformed the understanding of EC, leading to the identification of subtypes such as POLE-mutated, mismatch repair deficient, p53-abnormal, and no specific molecular profile. These classifications, now integrated into the 2023 FIGO staging system, allow for enhanced prognostic precision and individualized treatment

strategies. Such developments have shifted the focus from traditional, generalized approaches to precision oncology, ensuring more effective management tailored to each patient's specific tumor biology.

Despite these advancements, significant hurdles remain. Aggressive subtypes like p53-abnormal tumors continue to present poor outcomes, highlighting the need for innovative therapeutic approaches. Promising avenues include immunotherapies, molecularly targeted treatments, and predictive tools such as machine learning models and nomograms. These tools, which integrate clinical, molecular, and immune data, offer significant potential to refine risk assessment, optimize treatment decisions, and minimize overtreatment or undertreatment.

Moving forward, research must address the integration of molecular testing into routine clinical practice, improve the accessibility of advanced diagnostic methods, and develop novel therapies for high-risk subtypes. Additionally, special attention should be given to the needs of younger patients desiring fertility preservation. By combining these strategies with a commitment to individualized care, the field of gynecologic oncology is poised to achieve meaningful improvements in outcomes and quality of life for patients with EC.

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# Long Noncoding RNAs in Endometrial Cancer: Prognostic Biomarkers, Molecular Mechanisms, and Therapeutic Potential

*Harnoor Galani, Taranjit Kaur, Huzaifa Saqib, Daryl Traylor and Tamara Kalir*

## Abstract

Endometrial cancer (EC) remains the most prevalent gynecologic malignancy in developed countries. Recent insights into molecular biomarkers have highlighted long noncoding RNAs (lncRNAs) as critical players in cancer biology. LncRNAs are RNA molecules exceeding 200 nucleotides that regulate gene expression through diverse processes, such as post-transcriptional processing, transcriptional interference, and epigenetic changes. Several investigations identified lncRNAs such as HOTAIR, FER1L4, DLEU1, UCA1, PCAT1, and CARLo-5 as critical prognostic markers in EC. High-risk lncRNA expression profiles correlate with advanced FIGO stage, lymph node involvement, increased tumor grade, myometrial invasion, and distant metastasis. Mechanistically, lncRNAs participate in immune modulation, cuproptosis, epithelial-mesenchymal transition (EMT), and RNA epigenetic modifications (m6A). While lncRNAs present substantial prognostic potential, further validation and prospective studies are essential before clinical implementation. We included studies from multiple databases (PubMed, Google Scholar, etc.) from 2014 to 2025.

**Keywords:** long noncoding RNAs, endometrial cancer, prognostic biomarkers, molecular mechanisms, therapeutic targets

## 1. Introduction

Endometrial cancer (EC) is the most common malignancy affecting the female reproductive tract in developed countries, and its incidence is rising alongside obesity and metabolic syndrome prevalence [1, 2]. Prognostic assessment traditionally relies on histological subtype, tumor grade, depth of myometrial invasion, lymphovascular invasion, and the FIGO staging system [3]. Despite their clinical utility, these

parameters do not always adequately capture the biological and molecular diversity present in EC, resulting in imprecise patient stratification and management [4].

Molecular biomarkers have emerged to address this limitation, promising enhanced accuracy in prognosis and individualized therapeutic strategies. Among these molecular entities, long noncoding RNAs (lncRNAs) have attracted considerable attention. Defined as RNA molecules longer than 200 nucleotides that lack coding potential, lncRNAs regulate gene expression and cellular behavior at multiple levels, from epigenetic modifications to mRNA stability and protein interactions [5]. Their deregulation is frequently observed in cancers, including EC, impacting key processes such as proliferation, metastasis, apoptosis, and immune response [6]. Due to their stability and specificity, lncRNAs are attractive biomarkers for clinical prognosis and therapeutic intervention.

Multi-lncRNA risk signatures, which comprise a multitude of lncRNAs, also effectively stratify patients into diverse survival cohorts, showing moderate-to-high predictive accuracy (AUC typically between 0.70 and 0.85) across an abundance of investigations [6]. Collectively, these multi-lncRNA signatures supply robust prognostic indicators and offer insight into underlying biological processes such as immune evasion, cell death dysregulation, metabolism alteration, EMT, and epigenetic alteration, reporting encouraging directions for personalized therapeutic interventions in endometrial cancer.

This review synthesizes current research on lncRNAs in EC, highlighting their prognostic potential and elucidating the underlying biological mechanisms driving their effects on tumor progression and clinical outcomes.

## **2. Methodology**

A targeted literature review was conducted using PubMed and Google Scholar. The search was limited to peer-reviewed articles published between January 2014 and March 2025. An article was included if it evaluated the prognostic significance and molecular mechanisms of lncRNAs in EC.

## **3. Key oncogenic and tumor suppressor lncRNAs**

Recent research has consistently identified specific lncRNAs as key regulators of EC progression, prognostication, and potential therapeutic targeting, as shown in **Table 1**. Prominent oncogenic lncRNAs such as CARLo-5, PCAT1, UCA1, DLEU1, and HOTAIR have been repeatedly observed to be overexpressed in EC tissues, contributing significantly to tumor progression, invasion, and metastasis, whereas FER1L4 functions predominantly as a tumor suppressor.

Zhao et al. highlighted CARLo-5 as significantly upregulated in EC tissues compared to normal endometrium, correlating closely with advanced FIGO stage and lymph node metastasis. Patients exhibiting elevated CARLo-5 expression experienced notably poorer OS (OS; log-rank  $P = 0.003$ ), emphasizing its role as an adverse prognostic indicator. Additionally, CARLo-5 expression appears modulated by germline variation (rs6983267 SNP), suggesting a genetic basis for its oncogenic activity [7].

In subsequent studies, PCAT1 emerged as another highly relevant oncogenic lncRNA, significantly overexpressed in EC tissues. PCAT1 levels positively correlated

| lncRNA  | Expression in EC    | Associated clinicopathological features                                   | Prognostic impact                          | HR/AUC                  |
|---------|---------------------|---------------------------------------------------------------------------|--------------------------------------------|-------------------------|
| CARLo-5 | Upregulated         | Advanced FIGO stage; lymph node metastasis                                | Poor OS (P = 0.003)                        | —                       |
| PCAT1   | Upregulated         | Advanced stage; deep myometrial invasion; lymph node metastasis           | Independent predictor of poor OS           | HR = 3.012 (P = 0.011)  |
| UCA1    | Upregulated         | High grade; metastasis; lymphovascular invasion                           | Lower 5-yr OS (41.7% vs. 72.7%; P = 0.023) | —                       |
| DLEU1   | Upregulated (Serum) | Serous histology; high grade; advanced stage; lymphovascular invasion     | Poor OS & DFS                              | HR = 3.201; AUC = 0.883 |
| FER1L4  | Downregulated       | Advanced stage; distant metastasis; lymph node metastasis                 | Poor OS                                    | HR = 2.782 (P = 0.004)  |
| HOTAIR  | Upregulated         | High grade; deep invasion; lymphovascular invasion; lymph node metastasis | Poor OS                                    | —                       |

**Table 1.**  
*Summary of key lncRNAs in endometrial cancer and their clinical significance.*

with aggressive features, including advanced FIGO stage, deep myometrial invasion, and lymph node metastasis. Multivariate Cox regression confirmed PCAT1 overexpression as an independent predictor of worse prognosis (HR = 3.012, 95% CI: 2.796–3.623, P = 0.011), reducing OS among EC patients [8].

Similarly, Lu et al. demonstrated UCA1's significant overexpression in EC tissues, escalating further in metastatic disease. UCA1 correlated strongly with critical pathological parameters such as lymph node and distant metastasis, high tumor grade, and lymphovascular invasion. High UCA1 expression predicted a significantly lower 5-year survival rate (41.7% vs. 72.7%, P = 0.023), reinforcing its prognostic relevance. The authors also determined that silencing UCA1 by knocking down its expression in EC cell lines led to a significant reduction in the migratory and invasive ability of malignant cells (P < 0.05) [9].

DLEU1 was uniquely explored as a circulating biomarker by Shan et al. Serum DLEU1 levels were significantly elevated not only in established EC but also in atypical hyperplasia, signifying potential utility for early cancer detection. DLEU1 provided robust diagnostic accuracy, distinguishing EC patients from healthy controls with an excellent AUC of 0.883. Elevated DLEU1 also correlated strongly with aggressive disease phenotypes, such as serous carcinoma, advanced FIGO stage, high tumor grade, and positive lymphovascular invasion. Critically, high serum DLEU1 independently predicted poor overall and disease-free survival (HR = 3.201, 95% CI: 1.496–6.848, P = 0.003) [10].

Conversely, Kong and Ren identified FER1L4 as a tumor-suppressive lncRNA significantly downregulated in EC. Lower FER1L4 expression is closely associated with metastatic disease, lymph node involvement, and advanced FIGO stages. Reduced FER1L4 expression independently correlated with poor survival outcomes (HR = 2.782, 95% CI: 1.144–5.123, P = 0.004), highlighting its protective role in EC pathology [11].

HOTAIR, a well-characterized oncogenic lncRNA, was found significantly overexpressed in approximately 75% of EC cases studied by He et al., correlating with aggressive disease traits including high tumor grade, deep myometrial invasion, lymphovascular space invasion, and lymph node metastasis. Overexpression of HOTAIR independently predicted decreased OS ( $P < 0.05$ ), reinforcing its status as an important prognostic biomarker [12].

Collectively, these studies underscore the profound clinical and prognostic implications of specific lncRNAs in EC. Elevated expression of oncogenic lncRNAs (CARLo-5, PCAT1, UCA1, DLEU1, and HOTAIR) aligns closely with increased tumor aggressiveness, metastatic potential, and poorer patient survival. In contrast, loss of tumor-suppressor lncRNA FER1L4 similarly indicates an unfavorable prognosis. Emerging serum-based markers such as DLEU1 offer promising avenues for non-invasive diagnostic and prognostic assessment.

## **4. Multi-lncRNA signatures related to biological mechanisms in EC**

### **4.1 Immune-related lncRNAs**

In endometrial cancer (EC), immune-related long noncoding RNAs (lncRNAs) play a crucial role in regulating the tumor immune microenvironment and adaptive immunity [13–16]. Immune-related lncRNAs modulate T-cell infiltration, macrophage polarization, and expression of immune checkpoint molecules such as PD-L1 and CTLA-4. Mechanistically, these lncRNAs affect immune checkpoint expression, cytokine signaling, T-cell activation, and antigen presentation, creating an immune environment that favors tumor survival.

Impaired immunity can result from abnormal expression of specific lncRNAs, which can upregulate immune checkpoints like PD-1 and PD-L1, suppress cytotoxic T-cell infiltration, and increase regulatory T-cell (Treg) expansion [13–16].

Multiple studies have highlighted immune-related lncRNA signatures capable of stratifying EC patients based on prognosis and therapeutic responsiveness to immune checkpoint blockade therapies. To predict prognosis and immunotherapy responsiveness in EC, Meng et al. created an immune-related gene signature representing the immune activity within the tumor microenvironment [17].

Similarly, Liang and colleagues identified lncRNAs linked to pyroptosis that impact PD-1/PD-L1 signaling, an essential pathway in which tumors alter the immune microenvironment to prevent T-cell activation and promote immune evasion. In their comprehensive study, tumors classified into the low-risk group demonstrated higher sensitivity to immunotherapy, whereas those in the high-risk group were more likely to escape immune surveillance [18].

Furthermore, Sun et al. developed an immune-related lncRNA prognostic signature for patients with uterine corpus endometrial cancer (UCEC) and identified 13 lncRNAs that may predict OS. According to their model, immunological statuses varied across high- and low-risk groups, supporting that immune-related lncRNAs are crucial in predicting prognosis and immunotherapy responses in EC [19].

Prognostic models for endometrial cancer based on immune-related biomarkers have been developed recently. Zhang et al. combined immune cell infiltration patterns with tumor mutational burden (TMB) profiles to analyze TCGA data and create a 13-lncRNA signature. With a C-index of 0.78, their model predicted disease-free

survival and response to immune checkpoint therapy. The patients classified into the high-risk group experienced significantly worse outcomes [20].

Furthermore, Wang et al. used principal component analysis and Cox regression to find a 12-lncRNA signature. Their model demonstrated strong predictive power with a 5-year OS AUC of 0.831 and distinguished between patients at high and low risk based on survival outcomes. Age  $\geq 65$  years (HR = 2.069,  $p = 0.014$ ), FIGO stage III (HR = 3.231,  $p < 0.001$ ), stage IV (HR = 4.559,  $p < 0.001$ ), and lncRNA risk status (HR = 2.897,  $p = 0.004$ ) were all independent predictors of a worse prognosis in multivariate analysis. Patient age, tumor grade, and FIGO stage were significantly correlated with several lncRNAs, including AC103563.7, AL049539.1, ELN-AS1, NRAV, and POC1B-AS1. Altogether, these immune-related lncRNA signatures provide tools to improve patient outcome prediction and guide future endometrial cancer treatments [14].

Novel therapeutic approaches that target immune-related lncRNAs may enhance immunotherapy responses in EC by restoring T-cell-mediated immunity. Based on recent research by Xin and colleagues, lncRNA H19 is a therapeutic target that could improve immune-mediated tumor clearance. It is an essential regulator of immune cell infiltration and extracellular matrix remodeling in gynecologic malignancies. Therapeutic approaches such as RNA interference or epigenetic reprogramming that target lncRNA H19 may improve immunotherapy efficacy in EC, decrease immunosuppressive signaling, and restore T-cell infiltration [21]. Further studies of lncRNA-mediated immune modulation are necessary for developing more advanced immunotherapies.

## 4.2 Cuproptosis-related lncRNAs

Recent literature highlights cuproptosis as a unique copper-dependent cell death characterized by the buildup of mitochondrial proteins bound to copper, proteotoxic stress, and cellular death. Notably, various studies have found that tumor tissues in EC have higher levels of copper than standard samples, indicating that copper accumulation may play a role in carcinogenesis [22, 23].

According to Qi et al. and Wu et al., high intracellular copper causes cuproptosis by directly binding lipoacylated structures, which impairs mitochondrial activity and results in cell death [21, 24]. At the molecular level, the cellular response to copper stress is modulated by the abnormal production of lncRNAs. Cuproptosis-related lncRNA (CRL) signatures have been shown in multiple studies to be strongly associated with prognosis in EC, with increased probabilities of tumor burden, altered immune infiltration, and worse survival rates [22–25].

Significantly, lncRNAs impact mitochondrial respiration, energy metabolism, and immune function modulation [22–25]. Also, specific CRLs in high-risk populations are linked to lower CD8<sup>+</sup> T-cell infiltration and higher immune checkpoint expression [23, 24]. Furthermore, CRLs have been tied to vital processes such as oxidative phosphorylation, TCA cycle control, and immune response regulation [22, 23].

Interestingly, CRL expression patterns distinguished patients into different prognostic groups, each with unique tumor immune environments [22, 24]. Analysis of more than 550 endometrial cancer patients from the TCGA database in recent years has demonstrated that CRL-based signatures are a useful way to stratify patients into high- and low-risk categories. Cai and colleagues created a seven-lncRNA model linked to cuproptosis that was useful for predicting endometrial cancer patient outcomes. The low-risk group's patients had increased longevity and

better immunological responses, such as increased CD8<sup>+</sup> T-cells and type II interferon activity [25].

Qi et al.'s CRL prognostic model for endometrial cancer found high-risk patients with significantly poorer survival outcomes. Low-risk patients showed higher tumor mutation burden, greater CD8<sup>+</sup> T-cell infiltration, and increased immune responses. This may suggest improved immunotherapy outcomes [22].

Furthermore, He et al. found that necroptosis-related lncRNA profiles predicted greater sensitivity to anti-cancer agents such as vinblastine and olaparib, with risk score AUC values for overall survival reaching up to 0.717. Beyond its effects on prognosis, lncRNAs linked to cuproptosis and necroptosis are showing promise as therapeutic targets. Moreover, He et al. showed that high-risk EC patients were more susceptible to anti-cancer treatments such as vinblastine and palbociclib [26]. Furthermore, therapies that trigger programmed cell death may overcome resistance to some treatments and reestablish immune surveillance.

The recent data from the literature suggest that lncRNA signatures targeting cuproptosis and necroptosis can improve prognosis prediction and create metabolism-based treatments for EC.

### **4.3 EMT-related lncRNAs**

Biologically, epithelial-to-mesenchymal transition (EMT) describes a situation in which epithelial cells lose their polarity and cell-cell adhesion properties and become mesenchymal-like cells. This process plays crucial roles in physiological contexts, including embryonic development, wound healing, and pathological conditions, including fibrosis and cancer metastasis. EMT is characterized by the downregulation of E-cadherin, a crucial component of adherens junctions, and the upregulation of mesenchymal markers such as N-cadherin, vimentin, and fibronectin, along with increased expression of matrix metalloproteinases [27]. This nuanced biological process enables epithelial cancer cells to lose their intercellular connections and acquire mesenchymal traits, enhancing their migratory and invasive capabilities. EMT can also lead to the degradation of the extracellular matrix, drug resistance, acquisition of stemness, and enhanced invasion; it plays a crucial role in cancer progression and metastasis [28].

Clinically, several recent studies have proposed EMT-related lncRNA signatures as a prognostic tool for endometrial cancer. Jin et al. identified 5 EMT-related lncRNAs, namely RP11-295G20.2, RP11-469H8.6, AL022344.7, RP11-438B23.2, and LINC01224, which were significantly associated with overall survival and were used to build a prognostic model classifying endometrioid EC patients into high- and low-risk groups based on the expression of these five lncRNAs [29]. This risk score yielded ROC plot AUC values of 0.929, 0.939, 0.923 for 1-year, 3-year, and 5-year survival in the training set and 0.696, 0.885, and 0.674 in the testing set.

In a separate study, Shu et al. used 9 EMT-related lncRNAs, namely AL121906.2, HOXBAS3, AC017074.1, LINC00908, LINC01224, SCARNA9, LINC00957, AC083799.1, and AC080013.4, in their prognosis prediction model with a ROC plot AUC of 0.727. The lncRNAs included in this score also correlated with a significantly better (SCARNA9, LINC00908) or significantly poorer (AL121906.2, HOXBAS3, AC017074.1, LINC01224, LINC00957, AC083799.1, AC080013.4) overall survival individually. The high-risk group had an elevated rate of p53 mutations [30].

Despite these promising models, both Shu et al. and Jin et al. correlate their prediction scores with markers for immunotherapy response but yield very low correlation coefficients of  $-0.21$  for infiltration of CD8<sup>+</sup> T-cells or  $0.13$  for infiltration of macrophages and  $-0.1$  for correlation with an immune score, so further research is needed to address whether these prognosis prediction scores can also predict responses of EC to immunotherapy [29, 30].

However, there are hints that EMT-related lncRNA expression affects the response to different chemotherapeutics, as Shu et al. [30] observed a higher sensitivity to cisplatin and doxorubicin but a lower sensitivity to docetaxel in the high-risk group of their lncRNA expression prediction score.

#### 4.4 m6A-related lncRNAs

N6-methyladenosine (m6A) modification is the most common epigenetic modification of RNAs in eukaryotic cells [31]. m6A modification is established by methyltransferases, so-called ‘writers’ (e.g., METTL3, METTL14), and can be reversed by demethylases termed ‘erasers’ (e.g., ALKBH5). Functionally, this leads to the binding of m6A-modified RNAs to interacting RNA-binding proteins (RBPs), so-called ‘readers’ (e.g., YTHDF, IGF2BP, HNRNPC), influencing their downstream function. Like mRNAs, m6A modification of lncRNAs can affect their stability and binding to RBPs [32]. Additionally, m6A modification of lncRNAs can switch functions by influencing the lncRNA molecule’s secondary structure (e.g., hairpins) in a way that allows it to unfold and make certain regions accessible for binding partners or readers [33].

In cancer research, m6A modification of lncRNAs has been linked to the progression of different cancer types and gynecological cancers, more specifically [32, 34]. Liu et al. showed that m6A modification is downregulated in 70% of endometrial tumors, leading to increased cell proliferation, and AKT pathway activation [35].

Recently, there have been some approaches to using m6A-related lncRNAs as a prognostic tool in EC. Shi and colleagues identified three m6A-related prognostic RNAs, namely AL133243.2, SCARNA9, and TRAF3IP2-AS1, whose individual expression correlated with significantly better (SCARNA9) or poorer (AL133243.2, TRAF3IP2-AS1) OS of EC patients and which were used in a nomogram model to assess 3-year/5-year OS with an area under the curve (AUC) of  $0.793/0.816$  in the training groups and  $0.721/0.769$  in the validation groups in receiver operating characteristic (ROC) plots [36].

In another study, Shan et al. developed a risk score including AL645568.1, NNT-AS1, RAB11B-AS1, LINC01936, and HM13-IT1 as five prognostic m6A-related lncRNAs. This risk score correlated with significantly poorer OS and a higher pathological grade of EC patients. It reached ROC plot AUC values of  $0.74$  in the training and  $0.69$  in the validation group [37].

Similarly, Zhou et al. used a prognostic model including m6A-related lncRNAs RAB11B-AS1, LINC01812, HM13-IT1, TPM1-AS, SLC16A1-AS1, LINC01936, and CDKN2B-AS1, which reached an ROC-plot AUC of  $0.707$ , performing comparably well as a predictor of 1-year OS as the tumor grade (AUC  $0.648$ ) [38].

Additionally, Xie and colleagues described 5 m6A-related prognostic lncRNAs in uterine corpus endometrial cancer: LINC02043 expression was associated with a poorer prognosis with a hazard ratio (HR) of  $1.17$  and p-value (p) of  $0.011$ . In contrast, LINC00683 (HR  $0.865$ ,  $p = 0.006$ ), LNCTAM34A (HR  $0.759$ ,  $p < 0.001$ ),

FZD10\_AS1 (HR 0.845,  $p < 0.001$ ), and MIR497HG (HR 0.817,  $p < 0.001$ ) expression were associated with a better prognosis. The prognostic lncRNA-based risk score reached an AUC of 0.679, 0.681, and 0.713, predicting 1-year, 3-year, and 5-year OS [39].

Moreover, Qian et al. developed a risk score based on 5 m6A-, cuproptosis-, and ferroptosis-related lncRNAs, namely FZD10AS1, CDKN2B – AS1, LINC01480, BX322234.1, and SENCRCR, that was able to predict OS with an AUC of 0.692 at 1 year, 0.753 at 3 years, and 0.775 at 5 years. The m6A- and ferroptosis-related lncRNA CDKN2B-AS1 was associated with poorer prognosis, and the m6A-related lncRNA FZD10-AS1 with better prognosis [40].

However, there is a lack of studies systematically evaluating m6A-related lncRNAs as therapeutic targets in EC. Nevertheless, m6A-related lncRNA expression might influence the sensitivity to other drugs.

## **5. Limitations and future directions**

Current research heavily relies on retrospective datasets (particularly TCGA), with limited external or prospective validation, reducing the generalizability of findings. Clinical data annotations are often sparse, restricting deeper multivariate analyses. Experimental validation of lncRNA functions remains insufficient, leaving their exact biological roles unclear. Furthermore, varied statistical methods, inconsistent reporting standards, and different risk-score approaches make comparisons across studies challenging.

Future research should prioritize rigorous statistical analyses and methods. Validation in external, prospective, multicenter cohorts is essential to confirm clinical usefulness. Integrating multi-omics data and experimental validation will further enhance the biological credibility of identified lncRNAs. Finally, before adopting AI-based tools into clinical practice, thorough methodological validation is crucial. Addressing these recommendations will help improve the reliability and clinical impact of lncRNA-based prognostic research in endometrial cancer.

## **6. Conclusion**

lncRNA research in endometrial cancer has progressed from a specialized area of interest to a significant area of molecular oncology research over the last decade. Currently, our knowledge of tumor behavior centers upon these once-overlooked RNA transcripts, which influence immune responses, metastasis, cuproptosis, EMT, and m6A alterations.

Though there is promising research in the current review, it is evident that we are merely beginning to investigate the possibilities. The road to clinical translation is still paved with necessary validation work, and specific models need to be interpreted cautiously due to methodological limitations. However, there is genuine promise that lncRNAs could change how endometrial cancer is treated by providing earlier diagnosis, improved prognostic tools, and more individualized treatments. The renewed interest in lncRNAs reveals that the once-overlooked regions of the genome may hold some of the most promising insights for shaping the future of gynecologic oncology.

## **Additional information**

### **Human subjects**

This narrative review does not involve any human subjects or identifiable patient data. All data discussed are derived from previously published, peer-reviewed sources and are fully anonymized in accordance with the International Committee of Medical Journal Editors (ICMJE) guidelines and the ethical principles outlined in the Declaration of Helsinki.

### **Conflicts of interest**

The authors declare no conflicts of interest.

### **Payment/Services information**

Not applicable.

### **Financial relationships**

The authors have no financial relationships to disclose.

### **Other relationships**

All authors declare that they have no relationships, financial or otherwise, that could be perceived as influencing the content, objectivity, or conclusions of this review.

### **Data availability statement**

This is a literature-based review; no new datasets were generated or analyzed. References to all included studies are provided in the manuscript. Additional details or clarifications can be made available upon reasonable request to the corresponding author.

### **Data sharing statement**

Not applicable, as this review is based solely on publicly available, published literature and does not involve original patient data.

### **Author contributions**

Harnoor Galani contributed to conceptualization, methodology, data collection, writing, reviewing, and editing. Taranjit Kaur contributed to writing, reviewing, and editing. Huzaifa Saqib and Daryl Traylor contributed to editing. Dr. Tamara Kalir contributed to supervision, guidance, reviewing, and editing.

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## Section 4

# Menopause

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# Role of Nutrition in Menopausal Women

*Samiya Khan*

## Abstract

Menopause is a natural part of a woman's life that causes hormonal imbalance. This imbalance leads to the development of metabolic and inflammatory disorders. Previous studies have shown a high prevalence of obesity, cardiovascular disease, osteoporosis, and metabolic syndrome among these women. All of these disorders not only require medical attention but also need a nutrition care process. Nutritional assessment is an important step in the nutrition care process, helping to identify the nutritional status, identification of requirements, and aggressive intervention. On the basis of nutritional assessment, dietary modification, not just in terms of calories, protein, and fat, is required, but healthy lifestyle modification and increased physical activity are needed. Early nutritional intervention and lifestyle modification are helpful not only in the prevention of disorders but also in improving the quality of life and lengthening the lifespan of women.

**Keywords:** menopause, metabolic disorder, an inflammatory disorder, nutrition, lifestyle, physical activity

## 1. Introduction

Menopause, which marks one-third of a woman's life, is a significant period of aging. The postmenopausal phase is a stage where one experiences permanent cessation of the menstruation cycle over a year [1]. Decreased and complete cessation of hormone production affects the biological systems [2].

Due to aging and hormonal imbalance, there is an increased risk of developing metabolic disorders like obesity, diabetes, hypertension, and cardiovascular disease, as well as an increased risk of developing cancer that will affect the quality of life and decrease life expectancy [3].

In a recent review [4], they concluded that components of metabolic disorders such as central obesity, insulin resistance, and NAFLD/MAFLD are commonly seen in postmenopausal women. These factors are emphasized because they increase the risk of cardiovascular events and cause long-term health problems in middle-aged women after menopause. In these metabolic disorders, drug treatment is implemented, but lifestyle modifications, such as a calorie-restricted diet and increased physical activity, are also important for management and prevention [4].

As changes occur in the metabolism after menopause, that will also lead to changes in the nutritional requirements. Early nutritional intervention and changes in dietary

habits will also help to prevent the risk of developing metabolic and inflammatory diseases. In the present review, we investigate metabolic changes and the nutritional requirements of menopausal women.

## **2. Definition of menopause and metabolic changes**

### **2.1 Menopause**

Menopause is the phase of a woman's life that occurs between the ages of late 40s and early 50s, where women experience a complete cessation of menstruation resulting from a loss of ovarian follicular activity. During menopause, there is a loss of ovarian follicles, follicular development, and ovulation, resulting in the cessation of cyclical estrogen and progesterone production [5].

Menopause symptoms might persist beyond the FMP but usually begin during the menopause transition. Menstrual cycles become irregular due to declining and fluctuating hormone levels. Based on information from the British National Survey of Health and Development, Mishra and Kuh [6] characterized four symptom groups: somatic, vasomotor, psychological, and sexual discomfort. These symptoms occur due to an imbalance in hormones during menopause [6].

### **2.2 Metabolic changes in menopause**

Metabolism is the process of utilizing carbohydrates, protein, and fat obtained from food to gain energy in the body. Disorders in the metabolism of any macronutrient may lead to metabolic disorders or inflammatory disorders. The menopause transition may lead to changes in the composition of the body that may cause metabolic disorders [7].

#### *2.2.1 Changes in the body composition*

Hormonal imbalances after menopause may affect the woman's body at various levels. Estradiol hormone is released by the ovaries, but after menopause, the decreased production may affect the central nervous system, causing an increase in food intake and energy consumption. Low levels of estradiol also increase insulin resistance in skeletal muscles and increase gluconeogenesis in the liver [8].

Decreases and absences of estrogen due to the menopause transition cause decreases in the basal metabolism that increase the body weight and visceral fat mass, leading to obesity in women [9]. The increased consumption of energy causes an increased release of local growth factors that may cause increased production of free radicals by inducing excess metabolic activity and oxygen consumption. These free radicals may accumulate in the adipose tissue, causing structural damage. This leads to increased production of pro-inflammatory molecules, causing low-grade systemic inflammation [10].

#### *2.2.2 Changes in the lipid metabolism*

After menopause, decreased estrogen and estradiol levels increase the risk of developing cardiovascular disease significantly [11]. Estrogen and estradiol exert protective effects on lipid metabolism by releasing vasoactive compounds promoting vasodilation, nitric oxide, and prostacyclin [12]. They also play a role in the regulation

of the vascular system with anti-inflammatory and epigenetic-modifying effects. In general, an increased rate of deficiency of estrogen and estradiol will also cause a greater risk of developing hyperlipidemia and cardiovascular disorders [13].

2.2.3 *Changes in the carbohydrate metabolism*

During and after menopause, carbohydrate metabolism is also hampered by impaired insulin secretion and insulin sensitivity, resulting in an increased risk of hyperglycemia. Estrogen deficiency after menopause affects metabolism by decreasing insulin secretion in the pancreatic beta cells, and decreased insulin sensitivity in the muscles results in a decrease in glucose uptake. Increased insulin resistance in the liver causes an increase in gluconeogenesis and lipogenesis, increases lipid accumulation, and decreases insulin clearance. These changes lead to an increased risk of developing carbohydrate metabolic disorders or metabolic syndrome [14].

2.2.4 *Changes in bone metabolism*

Bone loss accelerates substantially in late perimenopause and continues at a similar pace in the first postmenopausal years. Bone mineral density begins to diminish gradually in both elderly men and women, but bone loss increases greatly in women after menopause. Loss of bone mass is the result of changes in the hormone-directed mechanisms that govern bone remodeling—any interruption of menstruation for an extended period results in bone loss. Estrogen- and androgen-deficient osteoporosis occurs in women within a few years of menopause because of a cessation of ovarian production of estrogens.

Estrogen promotes calcium absorption by enhancing the production of 1,25-dihydroxyvitamin D and also by having direct effects on the gut. Therefore, decreased estrogen levels lead to decreased intestinal calcium absorption after menopause. The typical bone loss in elderly females amounts to approximately 300 mg of calcium per day, which is lost in both the urine and the face. To maintain the calcium balance, this amount must be replaced by absorbed calcium from the diet each day. Calcium absorption depends largely on access to vitamin D (**Table 1**) [25].

| Study year and subject size                    | Study period | Conclusion                                                                                                                        | Vanpapendrop et al. |
|------------------------------------------------|--------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------|
| 2010, 1641 postmenopausal women                | 2 years      | High prevalence of obesity in postmenopausal women presenting to the fracture liaison service (FLS) with low-trauma fracture [15] | Premaor et al.      |
| 2017, 330 premenopausal and 265 postmenopausal | —            | Obesity was found more in postmenopausal women as compared to premenopausal women according to BMI, WC as well as WHR [16]        | Khokar et al.       |
| 2014, 50 postmenopausal and 50 premenopausal   | 10 month     | cardiovascular disease was more common in postmenopausal women than premenopausal women [17]                                      | Dosi r et al.       |
| 2005, 2576 postmenopausal women                | 4 years      | Postmenopausal women with osteoporosis are at an increased risk for cardiovascular events [18]                                    | Tankó et al.        |

| Study year and subject size                                                              | Study period | Conclusion                                                                                                | Vanpapendrop et al. |
|------------------------------------------------------------------------------------------|--------------|-----------------------------------------------------------------------------------------------------------|---------------------|
| 2013, reviewed data, 29,189 men, 6308 premenopausal women, and 4570 postmenopausal women | 10 years     | Postmenopausal state was significantly associated with the presence of dysglycemia [19]                   | Heianza et al.      |
| 2022, Survey review, 4968 postmenopausal women                                           | 7 years      | Premature menopause was associated with increased T2DM risk [20]                                          | Xing et al.         |
| 2017, 99,399 postmenopausal women                                                        | 22 years     | Prevalence of osteoporosis and fragility fractures in middle-aged women is hitherto under-recognized [21] | Boschitsch et al.   |
| 2007, 1642 postmenopausal women                                                          | —            | Osteoporosis is a prevalent disease among postmenopausal women [22]                                       | Lekamwasam et al.   |
| 2017, 958 women (aged 40–65 years)                                                       | 4 year       | Metabolic syndrome was more prevalent among postmenopausal women than among premenopausal women [23]      | Marchi et al.       |
| 2016, 350 women (aged 45–55 years)                                                       | —            | prevalence of MS is very high in postmenopausal women [24]                                                | Sharma et al.       |

**Table 1.**  
*Prevalence of metabolic disorders in menopausal women.*

### 3. Nutritional assessment of menopausal women

Nutritional assessment is the first step in assessing the nutritional status of the patient. After menopause, hormonal change leads to a decrease in basal metabolism in women's bodies which causes a decrease in basal metabolic rate (BMR) and an increase in body weight, typically gain in fat mass (visceral), therefore overweight and obesity commonly seen in women [26].

Also, due to hormonal changes, fat-free mass (FFM) and skeletal muscle mass (SMM) decrease, causing sarcopenia, an increase in fat mass, and a decrease in muscle

| Anthropometric measurements | Cut-off values | Classification             |
|-----------------------------|----------------|----------------------------|
| BMI (kg/m <sup>2</sup> )    | <18.5          | Underweight                |
|                             | 18.50–24.99    | Normal                     |
|                             | ≥ 25           | Overweight                 |
|                             | ≥ 30           | Obese                      |
| Waist circumference (cm)    | 64–80          | Normal                     |
|                             | 80–88          | Overweight (elevated risk) |
|                             | >88            | Obese (high risk)          |
| waist-to-hip ratio          | >0.80          | normal                     |
|                             | 0.80–0.85      | Moderate risk              |
|                             | <0.85          | High risk                  |

**Table 2.**  
*Classification of BMI, WHR, and WC.*

mass may lead to sarcopenic obesity [27]. Body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) help to determine obesity, which is a risk factor for metabolic disease [28]. However, these measurements do not provide information about body composition such as total fat mass or lean muscle mass. Therefore, for more accuracy, the use of a body composition analyzer is required (Table 2) [29].

## **4. Dietary recommendations**

Dietary intervention is significantly helpful in maintaining healthy nutritional status in peri and postmenopausal women. Nutritional intervention should be individualized to achieve healthy nutritional status. Lifestyle modification should be done for better outcomes.

### **4.1 Energy**

Energy requirements should be estimated, including the requirement for basal metabolic rate. A low-calorie diet of less than 1200 kcal will not be beneficial in weight loss and also lead to micronutrient deficiency. A very low-calorie diet of 800–1000 kcal does not show long-term effects [30]. The ideal rate of weight loss is 0.5–1 kg of body weight per week, which may occur due to loss of fat mass while maintaining muscle mass. Therefore, 500–1000 kcal lower energy should be provided than the current requirement, which makes it approximately 25 kcal/kg current body weight/day [31].

### **4.2 Carbohydrate**

In menopause, even in the absence of impaired glucose levels, it is important to maintain optimum nutritional status. Therefore, daily carbohydrate intake should be at least 120 g/day, which should include complex carbohydrate sources like fiber-rich vegetables, fruits, whole grain cereals, and pulses. Simple carbohydrate sources like sugar should not be more than 10% of daily energy intake [32]. Thirty to fifty grams of fiber intake daily is recommended, as it has the beneficial effect of slowing down carbohydrate uptake, gives the feeling of satiety, and helps in digestion. The approximate distribution of carbohydrates in each meal is important [33].

### **4.3 Protein**

Age-related changes in metabolism affect protein metabolisms. Insulin resistance is one effect of aging, which can lower skeletal muscle's ability to manufacture protein. To maintain muscle mass and lean body mass, daily protein intake should be 1–1.2 g/kg body weight/day, which is 20% of total energy. A diet with high protein content and low calories results in healthy weight loss that is loss of fat mass without losing muscle mass [34].

### **4.4 Fat**

The type of fatty acid is more important than the quality of fat in the diet. Saturated fatty acid intake should not be more than 10% of total fat intake, and saturated fatty acid should be replaced with polyunsaturated fatty acid. Increase dietary

intake of omega-3 such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as they have a protective effect against cardiovascular disease, decrease inflammation, and improve bone mineral density in menopausal women. Fat from vegetable oil is more recommended than animal and dairy [35].

#### **4.5 Micronutrients**

Vitamin D is essential for calcium absorption; therefore, dietary vitamin D intake is important. Aging decreases the hydroxylation of the precursor of vitamin D in the body, which leads to an increased requirement for vitamin D from diet. Vitamin D-rich food sources are egg yolks, dairy products, offal, and foods supplemented with vitamin D. Vitamin D supplementation reduces the risk of fracture in women taking treatment of osteoporosis. The recommended supplemental dose of vitamin D is 1000 IU per day [36].

Calcium requirements can be fulfilled by a balanced diet. Absorption of calcium primarily depends on the vitamin D status of the body. Dairy products, oil seeds, soft-bone fish, and food supplemented with calcium are the sources of calcium. If calcium deficiency is diagnosed, supplemental calcium can be used. The daily calcium recommended intake should be 1000–1200 mg for menopausal women [37].

Vitamin C plays an essential role in collagen formation; therefore, it is necessary for bone formation. The recommended daily requirement of vitamin C is 100 mg/day, which can be obtained from food. Its sources are fresh vegetables, fruits, and citrus fruits [38]. Vitamin B plays an important role in carbohydrate metabolism to generate energy, in the functioning of the nervous system, and reduces homocysteine levels, leading to a reduced risk of stroke and osteoporosis. A balanced vitamin B-rich diet plays an important role in menopause [39].

#### **4.6 Probiotic**

Decreased estrogen levels in menopause may affect the gut microbiota, causing dysbiosis and gastrointestinal complaints. Probiotic supplements are suggested in menopausal women. Probiotics reduce cardiovascular risk by maintaining the integrity of the intestinal barrier, therefore, reducing the translocation of bacteria through the gut wall and decreasing systemic inflammation. Probiotic ferment polysaccharides and undigested proteins to generate SCFA (i.e., acetate, propionate, and butyrate) in several metabolic pathways. The latest studies suggest that supplementation with probiotics improves cardiometabolic risk factors in postmenopausal women. Maintaining a healthy gut biome through a balanced diet according to the needs of menopausal women might help prevent dysbiosis [40].

#### **4.7 Physical activity**

Physical activity improves the metabolic risk factor and cardiovascular health. Physical activity reduces visceral fat mass, improves insulin sensitivity, decreases dyslipidemia, and reduces hypertension. M. Hyvärinen et al. [41], concluded that physical activity is associated with improved blood lipid profile and body composition in postmenopausal women. Therefore, physical activity like endurance exercise, strength exercise, and balance exercise can be recommended for menopausal women (Table 3) [41].

| Study year and subject size        | Study period | Conclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Vanpapendrop et al.  |
|------------------------------------|--------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| 2021, 393 postmenopausal women     | 4 month      | Higher-quality carbohydrate intake was found to be associated with lower somatic and psychological symptoms of menopause [42].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Mohsenian et al.     |
| 2022, 1204 postmenopausal women    | 4 years      | Higher intake of sucrose, or high glycemic load (GL) foods, may influence poor oral health outcomes in older women via their influence on the oral microbiome [43].                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Millen et al.        |
| 2016, 95 postmenopausal women      | 2 years      | A sedentary lifestyle and carbohydrate intake accounting for more than 55% of total energy intake were associated with higher body fat percentage and larger WC, as well as a higher odds ratio for cardiovascular risk [44].                                                                                                                                                                                                                                                                                                                                                                                                | Alves et al.         |
| 2014, 387 women (aged 60–90 years) | —            | Low protein intake group had a higher body fat and fat-to-lean ratio than those who consumed the higher protein diet [45].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Gregorio L et al.    |
| 2014 Review article                | —            | These findings suggest that healthy lifestyle measures in women aged >50 years are essential to allow healthy aging. ESCEO recommends optimal dietary protein intake of 1.0–1.2 g/kg body weight/day with at least 20–25 g of high-quality protein at each main meal, with adequate vitamin D intake at 800 IU/d to maintain serum 25-hydroxyvitamin D levels >50 nmol/L as well as calcium intake of 1000 mg/d, alongside regular physical activity/exercise 3–5 times/week combined with protein intake near exercise, in postmenopausal women for prevention of age-related deterioration of musculoskeletal health [46]. | Rizzolia et al.      |
| 2021, 4150 postmenopausal women    | 9 years      | The dietary omega-3 fatty acid intake in postmenopausal women was inversely proportional to depression in a dose–response manner [47].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Chae et al.          |
| 2011, 20 postmenopausal women      | 8 weeks      | Omega-3 fatty acids seemed to reduce depressive symptoms and vasomotor symptoms (VMS) in women who presented with major depressive disorder (MDD) related to the menopausal transition [48].                                                                                                                                                                                                                                                                                                                                                                                                                                 | Freeman et al.       |
| 2011, 79 postmenopausal women      | 2 years      | Long-term aerobic exercise training plus N <sup>-3</sup> supplementation have a synergistic effect in attenuating inflammation and augmenting bone mineral density (BMD) in postmenopausal osteoporosis [49].                                                                                                                                                                                                                                                                                                                                                                                                                | Tartibian et al.     |
| 2012, 54 postmenopausal women      | 3 months     | The multiple micronutrient supplements are effective in improving postmenopausal symptoms of hot flushes, night sweats, insomnia, depression, and tiredness and for improving the feeling of well-being [50].                                                                                                                                                                                                                                                                                                                                                                                                                | Pandit et al.        |
| 2017, 12 postmenopausal women      | 6 weeks      | Calcium and vitamin D are important to bone metabolism, and other micronutrients also make significant contributions to bone health [51].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Richardson CE et al. |

**Table 3.**  
*Meta-analysis on nutrients and their relationship with postmenopausal women.*

## 5. Conclusion

As per the above review, disorders like cardiovascular disease (CVD), obesity, diabetes, metabolic syndrome, and osteoporosis are commonly seen in menopausal women. Nutrition and lifestyle modification can reduce the risk of developing these diseases. Maintaining healthy weight and body composition is important in this phase to reduce the risk factors of developing abnormal metabolism in the body. Various meta-analyses have proved the effective role of nutrients in postmenopausal women. Many nutrients have proven to have preventive effects in reducing the risk of CVD, osteoporosis, obesity, diabetes, and other disorders. They also help in reducing the symptoms that many women experience during the phase of menopause phase. Intake of adequate amounts of calories, protein, carbohydrates, and micronutrients like calcium and vitamins D, C, and B is necessary. Complex sources of carbohydrates which are good sources of fiber should be included, and simple forms like sugars should be avoided or consumed in small quantities. High biological protein like poultry, fish, and low-fat dairy products, along with plant protein like beans, peas, lentils, chickpeas, soy, or dry fruits should be included in the diet. In fats and oil, preference should be given to vegetable fat, which is a good source of polyunsaturated fatty acid (PUFA) like omega-3 and animal fat should be avoided. Adequate intake of calcium and vitamins D, C, and B are required. Regular physical activity is also equally important.

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# Postmenopausal Hormone Replacement Therapy for Health Maintenance during Aging

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## Abstract

Several strategies have been proposed to prevent or reduce the rate of physiological decline in organ functions among aging postmenopausal women. These include increasing physical activity, improving nutrition, managing stress, and enhancing sleep quality. Although hormone replacement therapy (HRT) has been recommended, it remains a controversial topic, eliciting debate both in scientific circles and the public sphere. This book chapter aims to provide a comprehensive review of the current literature on the accelerated aging phenotype observed in postmenopausal women due to sex hormone deficiency. It will assess the efficacy and safety of HRT, offering a critical analysis of its benefits and risks. Moreover, the chapter will present a clinical perspective, suggesting practical advice for women approaching menopause. This guidance is intended for everyday clinical practice, aiming to support healthcare providers in offering informed, holistic care to this population.

**Keywords:** HRT, postmenopausal, health maintenance, sex hormone deficiency, cardiovascular system, brain, skin, bones

## 1. Introduction

Menopause signifies more than just the cessation of a woman's reproductive capabilities—it is a pivotal milestone in the female life cycle. This period heralds a range of significant physical transformations, often ushered in by challenging vasomotor symptoms (VMS) such as hot flashes and night sweats. Beyond these, a plethora of symptoms, including the genitourinary syndrome of menopause (GSM)—encompassing vaginal dryness, recurrent urinary infections, dysuria, and diminished libido—can severely affect a woman's quality of life. Moreover, menopause coincides with other age-related shifts in female biology, manifesting as notable two changes in the cardiovascular system, brain, skin, and bone. Intriguingly, many women perceive these changes as signs of “accelerated aging,” a sentiment frequently echoed in clinical settings where women express feelings of suddenly “getting old.”

This study supports the clinical observation that postmenopausal women exhibit accelerated aging phenotype. In the following, we will discuss studies that examined

postmenopausal biological changes in individual organs and the effects of hormone replacement therapy (HRT) on decreasing the “rate of aging.”

## **2. Search methods**

A search was conducted on PubMed for randomized clinical trials (RCTs) using a combination of terms: “hormone replacement therapy” OR “HRT” OR “hormone therapy” OR “HT” AND “cardiovascular disease” OR “CVD” OR “coronary heart disease (CHD)” AND “postmenopausal women.” This search extended across various organ systems. Additionally, a manual review of references was performed, specifically those cited in the book “Estrogen Matters” (2018) by Avrum Bluming and Carol Tavris [1], to identify relevant studies. To be included in the analysis, studies had to meet several criteria: (1) utilize a randomized controlled trial (RCT) design; (2) compare HRT with a placebo control; and (3) report both the relative risk (RR) and the 95% confidence interval (CI) for the comparison between HRT and placebo, along with the total number of participants in each group. A summary of the RCTs discussed in this chapter is included in **Table A1** in the Appendix.

## **3. Women exhibit accelerated aging during the postmenopausal period**

### **3.1 Postmenopausal cardiovascular system and HRT**

Cardiovascular disease (CVD) is the leading cause of death in both aged men and women [22]. Aging is associated with increased risk of atherosclerosis, hypertension, stroke, and atrial fibrillation [23]. Several studies have demonstrated that premenopausal women have a lower incidence of CVD when compared to age-matched males; however, the prevalence of CVD increases dramatically after menopause and women experience CVD 10 years later than men [22].

Murine animal studies have demonstrated that estrogen exerts cardioprotective effects including reduced oxidative stress, improved mitochondrial function, attenuation of cardiac hypertrophy, stimulation of angiogenesis, and vasodilation [24]. Estrogen deficiency leads to negative effects on the endothelium and vascular smooth muscle, decreases expression of nitric oxide (NO)-receptor soluble guanylate cyclase (sGC), decreases activation of vasodilator-stimulated phosphoprotein (VASP), enhanced sensitivity to vasoconstrictive agents and impaired vasorelaxation due to increased phenylephrine and angiotensin-II vasoconstriction effects through upregulation of angiotensin-II type I receptor, and changes in extracellular matrix (ECM) composition, all these changes lead to impaired vascular function and stiffening vessel walls as demonstrated in ovariectomized aging rats and that estrogen replacement attenuated these changes [25].

In humans, several RCTs have examined the role of HRT in the risk of CVD. In the following, we will discuss the main RCTs and contrast their findings. The most famous RCT is the Women’s Health Initiative (WHI) (1993) [2] which enrolled 27,347 postmenopausal women and aimed at examining the risks and benefits of HRT in postmenopausal women as a general “anti-aging” intervention measured by multiple outcomes (see **Table A1**, Appendix). The results of this trial have had enormous influence on clinical decision making regarding the use of HRT in postmenopausal women [2]. Specifically, postmenopausal women (age: 50–79 years and average

63 years) with a mean age of menopause of 12 years were randomized to receive in case of previous hysterectomy: conjugate equine estrogen (CEE) (oral dose 0.625 mg/day, N = 10,739) or placebo and in case of intact uterus: CEE in combination with medroxyprogesterone acetate (MPA) (oral 0.625 mg CEE + 2.5 mg of MPA/day, N = 16,608) or placebo. The “rate of aging” was determined by disease-specific endpoints: coronary heart disease (CHD) (primary outcome) and incidence of invasive breast cancer (primary safety outcome). Other outcome parameters measured included incidence of stroke, pulmonary embolism (PE), colorectal cancer, hip fracture, and death (measured by global index, GI) [2]. The details of inclusion and exclusion criteria are summarized in **Table A1** in the Appendix. The CEE + MPA trial was terminated after 5.6 years and CEE-only after 7 years due to safety concerns [26]. The WHI found a significant increase in CHD events: 29% increase in the CEE + MPA compared to placebo group. The increase was in nonfatal myocardial infarction (MI), with no significant differences observed in CHD deaths. In the CEE-alone group, there was a non-significant 9% reduction in CHD rates in the CEE group compared with placebo. It should be noted that a large percentage of women included in the WHI trial had CVD and were on treatment for the disease: 70% were overweight or obese (average BMI 28.5), >50% were current or previous smokers, and 48% of the women enrolled were receiving treatment for hypertension [2].

The WHI trial was followed by a number of clinical trials with a smaller number of participants. The Heart and Estrogen-progestin Replacement Study (HERS) [5] and HERS II [6] (see **Table A1**, Appendix) were designed to assess the efficacy and safety of HRT for secondary prevention of CHD events (nonfatal MI or CHD deaths) in postmenopausal women. In this study, 2763 women were enrolled and randomized to receive either CEE + MPA or placebo for 4 years. The mean age of participants was 66.7 years (85% > 60 years, 27% > 70 years) and approximately 20 years postmenopause (mean age at menopause was reported 48.7 years). The prevalence of coronary risk factors among the participants was high: 62% were past or current smokers, 59% had hypertension, 90% had serum LDL-cholesterol of 100 mg/dL or higher, 23% had diabetes, and about 34% were obese or severely obese and almost 20% were taking medications for treatment of CHD or for established risk factors associated with CHD. The trial did not reveal statistically significant differences between the randomized groups, suggesting that HRT is not effective in preventing secondary cardiovascular events in women with pre-existing CHD.

A newer study named Early vs. Late Estrogen Intervention Trial (ELITE) [16] examined the “timing hypothesis” stratifying the participants as early (<6 years) and late (>10 years) postmenopausal women (see **Table A1**, Appendix) and the women were randomized to either oral 17 $\beta$ -estradiol 1 mg/day or placebo for 5 years. The rate of carotid intima-media thickness (CIMT) progression (a marker for the extent of carotid atherosclerotic vascular disease) was significantly reduced in the early postmenopausal group assigned to estradiol compared to placebo. In the late postmenopausal group, CIMT progression did not differ between groups.

Another trial, Kronos Early Estrogen Prevention Study (KEEPS) [11], was designed to determine the effects of HRT in postmenopausal women on the progression of diseases in different organ systems including cardiovascular system (see **Table A1**, Appendix). A total of 727 healthy (free of subclinical CHD) women were included in the RCT and randomized for either oral CEE 0.45 mg/day (N = 230), transdermal estrogen (t-E2) 50  $\mu$ g/day (N = 222) or placebo (N = 275) for 4 years. The women were recent menopause and within 6 months to 3 years of natural menopause.

The primary outcome was the progression of subclinical atherosclerosis measured by CIMT. The trial reported a similar increase in CIMT across all three groups.

The difference in outcome between ELITE [16] and KEEPS [11] trials may be related to the duration of the intervention, sample size, and duration of the follow-up period being too short to be able to detect between-group differences. Also, there were differences in the dose and type of estrogen used: 0.45 oral CEE (KEEPS) compared with oral 17 $\beta$ -estradiol 1 mg/day (ELITE). However, KEEPS and ELITE trials demonstrate the safety of using HRT in postmenopausal women when employed within 6 years of menopause, without pre-existing CVD risk factors, and with an average treatment duration of 5 years.

Another study, The Danish Osteoporosis Prevention Study (DOPS) [18], examined 1006 healthy, younger, early postmenopausal women (in average 0.7 years postmenopause) in a 10.1-year RCT and subsequent unblinded follow-up for 6 years in order to determine the long-term effects of HRT (see **Table A1**, Appendix) [18]. They found that long-term HRT significantly decreased heart failure, MI, and mortality, which was maintained during an additional 6 years of non-randomized follow-up (HR 0.48, 95% CI: 0.26–0.87). However, the trial is relatively small, with small number of outcome events.

One contentious issue related to the effect of HRT on cardiovascular health is the role of progesterone supplementation. Thus, the postmenopausal Estrogen/Progestin Interventions (PEPI) trial [9] assessed the effects of HRT on CVD risk factors using different forms of progesterone (see **Table A1**, Appendix). In this trial, 847 healthy postmenopausal women were randomly assigned to one of the following groups: (1) placebo; (2) CEE 0.625 mg daily; (3) CEE 0.625 daily plus MPA 10 mg, days 1–12; (4) CEE 0.625 daily plus MPA 2.5 mg daily; or (5) CEE 0.625 daily plus micronized progesterone (MP) 200 mg, days 1–12. The outcomes assessed were HDL-C, systolic blood pressure, serum insulin and fibrinogen, and thromboembolic events [9]. The investigators reported a significant increase in HDL-C and a decrease in LDL-C serum levels across all treatment groups compared to placebo. Interestingly, women who received CEEs or CEEs/MP had significantly increased serum levels of HDL-C compared to CEEs/MPA group. There were no significant differences in the observed changes in systolic blood pressure and serum insulin levels, but fasting glucose levels significantly decreased in all treatment groups. Women assigned to placebo had a greater increase in serum levels of fibrinogen compared to the active treatment group, but there was no increase in adverse thromboembolic effects [9]. This study suggests a protective role of progesterone on CVD risk factors by improving lipoprotein profile and that MP may have a greater benefit than MPA.

### 3.2 Postmenopausal brain and HRT

The most common neurodegenerative disease is Alzheimer's disease (AD), and almost two-thirds of Americans with AD are women [27] and also the incidence rates of different forms of dementia and AD are greater in women than men [28, 29]. The increased risk of AD in postmenopausal women suggests that sex hormone deficiency is a significant risk factor [30]. This notion is supported by *in vitro* and *in vivo* studies.

In animal experiments, ovariectomy (OVX) leads to accelerated brain aging evidenced by reduced dendritic spines, decreased synaptic density, decreased number of synapses and a reduction in gray matter volume and the reverse effects with an increase in hippocampal dendritic spine and synapse density were observed following exogenous estrogen administration [31]. OVX studies in rodents have also shown that

long-term estrogen deficiency causes impairment of memory and learning abilities [32–34] as well as declines in the performance of both cognitive and motor tasks, short- and long-term non-spatial and spatial memory, cognitive impairment, and increased anxiety [34, 35].

Several of the abovementioned clinical trials in humans (see **Table A1**, Appendix) examined the effects of HRT on brain and cognitive functions. The KEEPS study [11] included an ancillary study that examined the effects of HRT on brain functions (KEEPS-Cog) [14] and reported that 4 years of HRT did not exert harmful or beneficial effects compared to placebo. The WHI [2] performed an ancillary study, The Women's Health Initiative Memory Study (WHIMS) [3], assessing the role of CEE or the combined CEE + MPA on the incidence of dementia and mild cognitive impairment (MCI) in older postmenopausal (aged 65–79) women (see **Table A1**, Appendix). After a mean follow-up of 4.2 years, 61 women in total were diagnosed with probable dementia: 40 among women assigned to CEE + MPA therapy relative to 21 in the placebo group. After restricting analyses to those adherents to therapy, the number of probable dementia cases was reduced to 21 in the CEE + MPA group; however, it still significantly increased relative to six in the placebo group. There were no statistically significant differences in MCI between the groups [3]. However, the increased risk of dementia was apparent already 1 year after randomization in both the CEE + MPA and placebo groups, suggesting that some participants had cognitive impairment at baseline and that CEE + MPA therapy may have accelerated pre-existing cognitive decline.

Another ancillary study to the WHI [2] was published in 2004 and is known as the Women's Health Initiative Study of Cognitive Aging (WHISCA, see **Table A1**, Appendix) [4]. WHISCA assessed the efficacy of postmenopausal HRT on longitudinal age-related changes in specific cognitive functions that included memory, cognition (measured by language, attention, and spatial ability), motor function, and mood in 2302 women aged 66–84 years (a mean of 12 years since menopause) who did not meet criteria for dementia at baseline and received treatment period for 3 years [4]. Women assigned to CEE + MPA had a negative impact on verbal memory over time and CEE-alone was associated with lower spatial rotational ability compared to placebo [36].

The ELITE trial [16] also included an ancillary study, ELITE-Cog, examining the effect of HRT on cognitive functions (see **Table A1**, Appendix) [17]. A total of 455 postmenopausal women participated in the study for 5 years (80% adherence). Neither early (<6 years) nor late (>10 years past menopause) initiation of HRT altered verbal memory, executive functions, or global cognition as assessed after a mean treatment duration of 57 months of oral 17 $\beta$ -estradiol combined with progesterone. While the study did not reveal positive effects on cognitive functions, it supports the safety of HRT use on cognition as no adverse effects on cognitive abilities were observed during the 5-year period of the study.

### 3.3 Postmenopausal skin and HRT

The first signs of dermal aging (skin thinning, folds, or wrinkles) start around 30–35 years of age when estrogen levels start to decline. Several RCTs have reported that CEE and estradiol (E2) formulations increase the thickness of the skin and of the dermis and therefore decrease the rate of skin aging [37, 38]. Oral E2 has also been demonstrated to increase skin elasticity and hydration [38]. An ancillary skin study of the KEEPS trial [11] (see **Table A1**, Appendix) examined the effects of HRT on wrinkles (assessed on the face and neck) and skin rigidity (assessed in forehead and

cheek) in postmenopausal women (age 42–58 and within 36 months of last menstrual period) of varying race/ethnicity [15]. Interestingly, there were no significant differences in the number and depth between women randomized to oral CEE, t-E2, or placebo during the 4-year follow-up period [15]. The timing of initiation of HRT seems to play an important role in preventing skin aging as it has been observed in a subgroup analysis that beneficial effects of HRT were observed when HRT was initiated within 24 months of the last menstruation [39]. Another study included 485 postmenopausal women in a 48-week RCT to assess the effects of low-dose HRT on postmenopausal skin changes, primarily facial wrinkling [39]. The women were randomly assigned to one of three interventions: placebo (165 subjects), 1 mg norethindrone/5 µg ethinyl estradiol (162 subjects), or a 1 mg norethindrone/10 µg ethinyl estradiol group (158 subjects) given orally. The participants were, on average, 53.6 years old and approximately 5 years postmenopausal. After 48 weeks, the investigators did not detect clinically significant differences between the groups; however, a subgroup analysis revealed marginal improvement in women who were less than 24 months in postmenopausal age [39].

### **3.4 Postmenopausal skeleton and HRT**

A large body of literature in both animal models and humans has demonstrated that estrogen deficiency leads to accelerated bone loss, increased bone resorbing osteoclastic activity, and impaired bone formation [40]. Similar effects were observed in OVX mice [41] and sheep [42]. Also, in human observational studies, postmenopausal period results in accelerated bone loss in both trabecular and cortical bone, leading to an increased risk of fracture [43]. Multiple mechanisms have been identified for the positive effects of estrogen on the postmenopausal skeleton, including inhibition of bone resorption, enhancing bone formation, and exerting positive calcium balance on the kidney and intestine [44].

Several human studies have consistently demonstrated the efficacy of HRT in preventing postmenopausal hormone loss and decreased risk of osteoporotic fractures. In the following, we will provide some examples of the most important human trials.

A 2-year open trial [45] of young healthy non-obese postmenopausal women (mean age 56.6 years) received a low dose (LD) continuous combined HRT (containing 1 mg estradiol +0.5 mg norethisterone acetate (NETA), or 0.5 mg of 17β-estradiol and 0.25 mg of NETA (ultra-low dose, ultra-LD-HRT), along with 1000 mg calcium daily or control group that received 1000 mg calcium/day for 2 years. At the end of the trial, the control group experienced a significant decrease in BMD at the spine ( $-2.8 \pm 0.2\%$ ) and femoral neck ( $-2.8 \pm 0.7\%$ ), whereas in the LD-HRT treated group, bone mineral density (BMD) showed a significant increase at the spine ( $5.2 \pm 0.7\%$ ) and femoral neck ( $2.8 \pm 0.4\%$ ). In the ultra-LD-HRT treated women's spine and femoral neck, BMD showed a significant increase ( $2.0 \pm 0.3$  and  $1.8 \pm 0.3\%$ , respectively [45].

The PEPI trial [9] (see **Table A1**, Appendix) compared changes in BMD in women assigned to different treatment groups as described previously and reported a significantly increase in BMD in women assigned to HRT compared to placebo at 12 and 36 months. The participants assigned to placebo lost an average of 1.8% of spine BMD and 1.7% of hip BMD, while those assigned to HRT exhibited 3.5% to 5.0% increases in spinal BMD and a 1.7% increase in hip BMD [10].

The relative contribution of progesterone and estrogen to the observed positive effects of HRT on bone mass was examined in a systematic review and meta-analysis

of five RCTs [46]. The analysis includes women (N = 1058) mid-50 years of age, early in menopause (<5 years except one study with average 12.8 years postmenopause) and found that CEE + MPA significantly increased annual percent spinal BMD gains (+0.68%/year; 95% CI: 0.38, 0.97%) relative to the same dose of CEE-alone suggesting beneficial additive effects of progesterone to estradiol in gain of spinal BMD [46]. Interestingly, one study examined dose–response effects of 10 or 20 mg of MPA 15 days/month together with estrogen and reported that a higher dose of MPA (20 mg) did not lead to further increase in spine and hip BMD after 1 year of treatment [47] suggesting that higher doses of MPA may not have an additive effect [46].

The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial (N = 822) examined the effects of lower doses of CEE + MPA on BMD in women aged 40–65 years within 4 years of menopause [48]. Women were randomly assigned to receive one of eight treatment regimens: (1) CEE 0.625; (2) CEE 0.625 + MPA 2.5; (3) CEE 0.45; (4) CEE 0.45 + MPA 2.5; (5) CEE 0.45 + MPA 1.5; (6) CEE 0.3; (7) CEE 0.3 + MPA 1.5 (all mg/day); or (8) placebo (calcium 600 mg/day). Women assigned to all of the active treatment groups had significant gains in BMD from baseline in spine and hip BMD as well as total body BMD after 24 months and also when compared to the placebo group. CEE 0.625 + MPA 2.5. Also, the study reveals differences in the incremental increase in BMD among intervention groups, suggesting the existence of an optimal dose-dependent effect of HRT with respect to the prevention of postmenopausal bone loss. In the CEE-alone group, CEE 0.625 had the greatest increase in hip BMD; however, in the CEE + MPA group, the CEE 0.45 + MPA 2.5 had the greatest increase in hip BMD [48].

The Danish RCT DOPS [18] (see **Table A1**, Appendix), which also examined the fracture-reducing potential of long-term HRT in recent postmenopausal women in a primary preventive scenario, reported a significant reduction in both the overall fracture risk (HR 0.61; 95% CI: 0.39–0.97) and the risk of forearm fractures (HR 0.24; 95% CI: 0.09–0.69) [19].

Finally, the WHI trial [2] (see **Table A1**, Appendix) showed significantly reduced hip and vertebral fractures as well as total osteoporotic fractures in both CEE-alone and CEE + MPA groups.

### 3.5 HRT and breast cancer

One of the major concerns of postmenopausal women considered HRT is the perceived increased risk for developing breast cancer. This issue has been examined in several RCTs. The WHI trial [2] was halted 3 years prior to the scheduled end due to the evidence of increased risk for breast cancer. The estimated HR for breast cancer was 1.26 (95% CI: 1.00–1.59), with 290 cases equivalent to a non-significant 26% reported increase in breast cancer (38 vs. 30 per 10,000 person-years). Interestingly, the WHI CEE-alone arm exhibited a non-significant reduction in incidence of invasive breast cancer. The HR was 0.77 (95% CI: 0.59–1.01) with 218 cases (26 in CEE-alone arm vs. 33 in controls per 10,000 person-years) [2]. An overview of WHI is provided in **Table A1** in the Appendix, and **Table 1** illustrates the main findings related to risk of breast cancer.

Several investigators were concerned that the presence of several confounders that affect the external validity of the WHI results as the study cohort comprised large percentage of women with chronic diseases and with a mean of 12 postmenopausal age and thus do not represent early and healthy postmenopausal women interested in

| Clinical trial                                                                                                                                                                                                                            | Outcomes assessed                                                                                                                                                                  | Main outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Conclusion                                                                                                                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Women's Health Initiative trial, CEE alone.<br>Stefanick et al., 2006 [49]                                                                                                                                                                | Breast cancer incidence among women assigned to CEE therapy relative to placebo.                                                                                                   | All breast cancer incidents diagnosed through February 29, 2004, were included in a re-analysis with mean follow up of 7.1 years. Invasive breast cancer HR for women assigned to CEE compared with matched placebo was 0.8 (95%-CI: 0.61–1.04). After one year, 9.2% of women in the CEE had mammograms with abnormalities relative to 5–5.5% in the placebo group which persisted through the trials, however the differences were only requiring short term follow up and were not suspicious or abnormal findings.                                                                        | Treatment with CEE alone does not increase incidence of breast cancer among postmenopausal women with prior hysterectomy.                                                                                       |
| Re-analysis of data from the combined WHI trials (N = 16,608) and a corresponding observational study cohort of women with an intact uterus who were either HRT users (N = 6,756) or non-users (N = 32,328).<br>Prentice et al., 2008 [8] | Relation between prior use of HRT and time from menopause to first use of HRT ("gap time") to risk of invasive breast cancer among women assigned to CEE +MPA compared to placebo. | A small but statistically significant elevated risk of breast cancer was detected among women randomized to CEE +MPA treatment compared to placebo (HR 1.96 vs 1.02). For women initiating treatment <5 years after menopause: HR for CEE+MPA 2.06 versus 1.77 in placebo. For women initiating treatment ≥5 years after menopause: HR for CEE+MPA 1.30 versus placebo 0.99. HR for women initiating HRT immediately following menopause (gap time 0), breast cancer risk was elevated during the first two years of CEE+MPA use and decreased to HR 0.84 with a five-year increment in time. | The WHI clinical trial and observational study each reveal an increased breast cancer risk of daily 0.625 mg CEE + 2.5 mg MPA. Women who initiate treatment soon after menopause appear to have increased risk. |
| Extended follow-up (median 11.8 years) of the WHI CEE-alone trial.<br>Anderson et al., 2012 [20]                                                                                                                                          | Breast cancer incidence and mortality among postmenopausal women with hysterectomy assigned to either CEE alone or placebo.                                                        | Women randomly allocated to CEE therapy (mean 5.9 years) had a lower incidence of invasive breast cancer (151 cases, 0.27% per year) than those receiving placebo (199 cases, 0.35% per year) with no differences between intervention and post-intervention phase effects. Performing subgroup analyses, the breast cancer risk was reduced in the CEE group in women without benign breast disease or family history of breast cancer. Fewer women died from breast cancer relative to controls (6 vs 16 deaths per year).                                                                  | 5-years of treatment with CEE therapy is associated with lower incidence of breast cancer and decreased mortality among women without benign breast disease or family history of breast cancer.                 |

| Clinical trial                                                                                                   | Outcomes assessed                                                                                                                                                     | Main outcomes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Conclusion                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Extended follow-up (median 13 years through September 2010) of the two WHI trials. Chlebowski, et al., 2015 [21] | Influence of long-term HRT on breast cancer incidence rates and breast cancer characteristics during intervention and during early and late post intervention phases. | Treatment with CEE+MPA compared to placebo led to an increase in total (245 vs 185 cases, HR 1.24,) and invasive (199 vs 150 cases, HR 1.24) breast cancers. Short-term CEE +MPA use increases incident cancers which then substantially drops in risk in the early post intervention phase (within 2.75 years from intervention), however the risk remains elevated in the late post intervention follow-up (mean 5.5 years) and the HR for breast cancer risk remains elevated (HR 1.37; 95%-CI: 1.06–1.77). The breast cancer risk reduction seen in the CEE alone trial during intervention was lower than 1 throughout the 7.2-year intervention phase and in the early postintervention phase the HR for the influence of CEE alone on breast cancer risk was substantially lower (HR 0.55; 95%-CI: 0.34–0.89). | With longer follow-up of the 2 WHI trials, a complex pattern of changing incidence of breast cancer was observed. Combined CEE+MPA increased the risk of breast cancer during the initial intervention followed by a substantial drop in risk in the early postintervention period, but with sustained higher breast cancer risk during late postintervention phase. Use of CEE alone reduced breast cancer risk through cumulative follow-up of 13 years. |

CEE = conjugated equine estrogen; HR = hazard ratio; HRT = hormone replacement therapy;  
MPA = medroxyprogesterone acetate.

**Table 1.**  
*Findings related to breast cancer risk as reported by the Women’s health initiative (WHI) trial.*

HRT [50]. Also, it should be noted that the WHI trial reported a 32% reduction in breast cancer risk, after 7.2 years of follow-up in CEE-alone group when analyses are limited to a minimum of 80% compliance (HR 0.67; 95% CI, 0.47–0.97). Also, across all women, regardless of compliance, ductal carcinoma was significantly reduced by 29% in the CEE-only arm relative to placebo, and 18 years of cumulative, breast cancer mortality was significantly reduced by 45% (HR 0.55; 95% CI: 0.33–0.92) [50].

Another important confounder is the extraordinarily low breast cancer incidence in the placebo group that had prior HRT use, which arguably falsely gives the impression that the elevated HR of breast cancer risk was caused by CEE + MPA treatment [50]. The reason behind the low breast cancer incidence in the subgroup is not clear; however, it has been externally validated as an outlier with WHI observational data [50].

Interestingly, other interventional trials, PEPI [9], HERS [5, 6], Women’s Estrogen for Stroke Trial [51], ELITE [16], DOPS [18], and REPLENISH [52, 53], did not reveal an increase in breast cancer incidence (see **Table A1**, Appendix). In fact, DOPS [18] reported that after 10 years of HRT intervention and subsequent 6 years of unblinded follow-up, women aged 45–58 years (mean of 49.7 years) had significantly reduced risk of breast cancer relative to placebo with HR 0.49 (95% CI: 0.28–0.87) in women with intact uterus and HR 0.42 (95% CI: 0.18–0.97) in women who received estrogen

alone [18]. Based on all these trials, it seems that HRT is generally safe with respect to breast cancer development when initiated in the early postmenopausal period and in healthy women.

#### **4. A practical approach for hormone replacement therapy in the postmenopausal period**

HRT is approved by US Food and Drug Administration (FDA) as an effective treatment for menopausal symptoms, for prevention of osteoporosis, and for treatment of premature ovarian failure [54]. Based on the results from RCTs discussed in the previous section, we will provide practical information regarding HRT use in postmenopausal women.

##### **4.1 Translation of clinical evidence to practical advice**

HRT is useful for treating the VMS associated with menopause, as supported by multiple studies [9, 52, 53]. However, advice regarding the long-term use of HRT for prevention of age-related diseases should be individualized, as shown in decision tree (**Figure 1**).

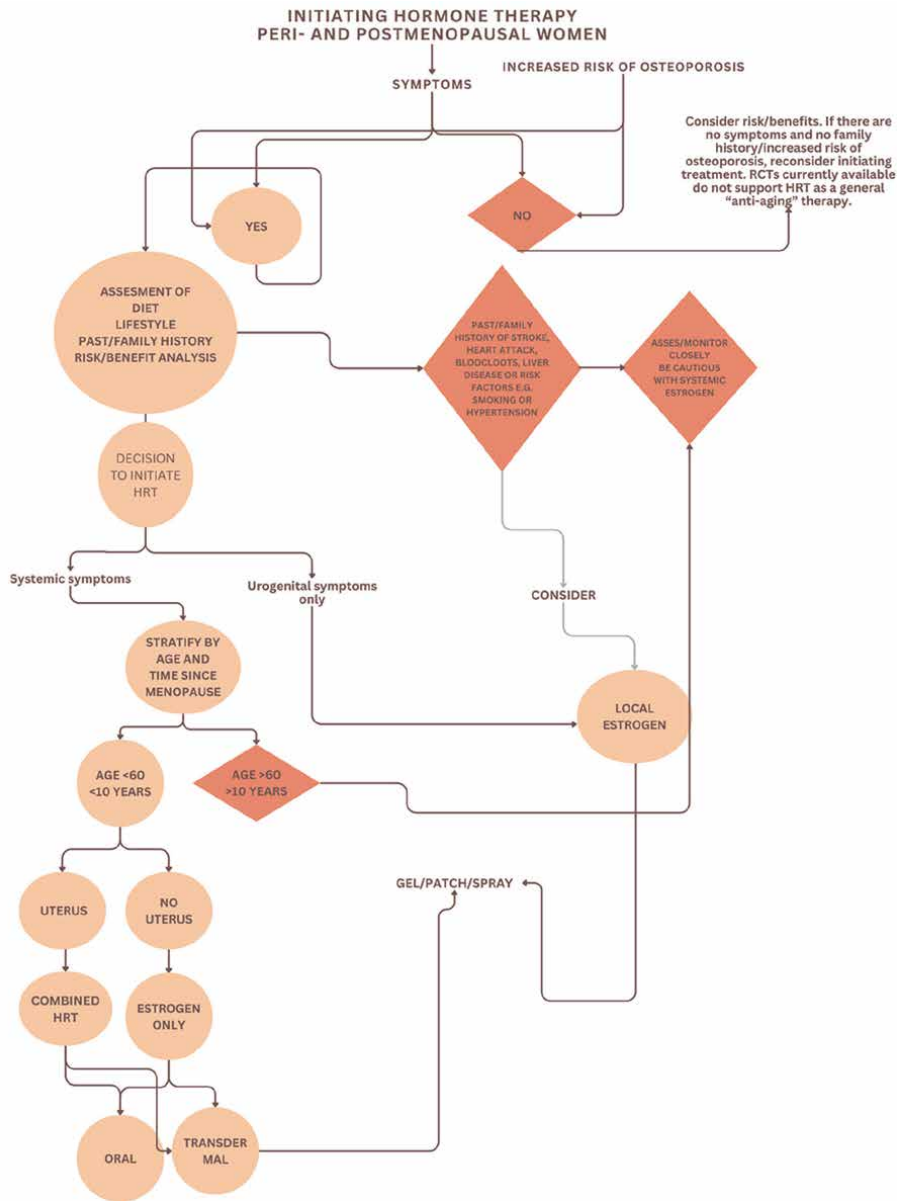
HRT can be employed in women with increased risk for osteoporosis as a preventive measure for bone loss and also when other standard medications are not chosen, e.g., bisphosphonate. While it is possible that HRT initiated early in the postmenopausal period may prevent CHD and maintain brain health, HRT is not recommended as an adjuvant treatment to decrease the rate of complications in women suffering from CHD or cognitive impairment. It is recommended to identify the most appropriate regimen, dose, duration, and route of administration, with periodic reevaluation of the benefits and risks of continuing or discontinuing HRT, based on individual preferences. Women who are overweight, smokers, have hypertension, diabetes mellitus, or suffer from other comorbidities including vascular or liver disease must be closely assessed prior to initiating treatment, particularly as women with these risk factors are often excluded from participation in RCTs and therefore their benefits and risks from HRT are less known.

##### **4.2 How do we inform women regarding the side effects of HRT?**

Women have concerns when starting or continuing HRT regarding possible side effects and, most importantly, concerns related to the increased risk of developing breast cancer. We think that HRT should be offered for healthy women without a family history of breast cancer or a previous history of heart disease, stroke, or breast cancer. In these women, starting therapy early in the postmenopausal period (< 5 years) is safe, as supported by findings from several trials: WHI [2], PEPI [9, 10], KEEPS [11], ELITE [16], and DOPS [18] that revealed no increase in thromboembolic disease, stroke, or breast cancer.

##### **4.3 Duration of therapy? control during therapy?**

The decision regarding the duration of treatment and when to stop HRT must be considered in the context of the individualized risk/benefit profile as well as personal preferences. It is not yet known if ongoing HRT by healthy women who initiate



**Figure 1.**  
*Decision tree, a practical approach to initiating HRT in peri- and postmenopausal women.*

treatment in early postmenopausal years (<5–10 years) but are now older than 60 years carries the same risk as initiating HRT in women with more than 10 years of postmenopausal age or older than 60 years. HRT does not need to be routinely discontinued in women aged older than 60 or 65 years, especially in women with persistent VMS, quality-of-life issues, or receiving HRT for prevention of osteoporosis [55].

Regular reassessment of the woman's health status (comorbidities, risk factors for CVD, and venous thromboembolism (VTE)) is necessary to ensure that the risks of continued treatment do not outweigh the benefits in each individual woman.

## 5. Conclusion and future directions

While several observational studies have reported the benefit of HRT in the prevention and treatment of chronic diseases such as CVD and dementia and in reducing all-cause mortality among postmenopausal women using HRT compared to nonusers [50], the results of RCTs did not provide unequivocal answers. However, the current literature regarding HRT in postmenopausal women has revealed the limitations of the benefits of using HRT as a general “anti-aging” strategy. HRT may be useful in a group of postmenopausal women with severe menopausal symptoms that reduce their quality of life and prevent postmenopausal bone loss. While more studies are needed to compare different routes of administration, regimens, and doses, physicians can currently provide postmenopausal women with balanced information regarding the risks and benefits of HRT to allow them to make an informed decision.

## A. Appendix

See Table A1.

| Clinical trial                                                                                                               | Outcomes assessed                                                                                                                                                                                                                                                                                                                                                                  | Inclusion criteria                                                                                                                                                                                                    | Intervention                                                                                                                                                                                                                                                                                                          | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Women’s Health Initiative (WHI) clinical trials</b><br>Writing Group for the Women’s Health Initiative Investigators, [2] | Two parallel, double-blinded RCT’s to determine whether HRT delays the rate of aging in postmenopausal women.<br>Primary outcome: Coronary heart disease (CHD) and incidence of invasive breast cancer (primary safety outcome).<br>Other outcomes include incidence of stroke, pulmonary embolism (PE), venous thromboembolism (VTE), colorectal cancer, hip fractures and death. | N = 27,357 postmenopausal women.<br>Age: 50–79 years (average 63 years), with a mean of 12 years since menopause.<br>70% were overweight or obese (average BMI 28.5).<br>>50%: current or previous smokers (N=8,237). | Women with intact uterus:<br>CEE+MPA<br>(1) 0.625 mg CEE +2.5mg MPA/day (N = 8,506);<br>(2) placebo (N = 8,102).<br>Women with prior hysterectomy:<br>(1) 0.625 mg CEE/day (N = 5,310);<br>(2) placebo (N = 5,429).<br>July 2002: CEE +MPA study was halted 3 years early.<br>March 2004: CEE alone study was halted. | 1. Breast cancer: HR was non-significant 0.77 (95%-CI: 0.59-1.01) with 218 cases (26 vs 33 per 10,000 person-years in CEE alone. HR for breast cancer were 1.26 (95%-CI: 1.00–1.59) with 290 cases equivalent to a 26% reported increase in breast cancer (38 vs 30 per 10,000 person-years) observed in the CEE +MPA.<br>2. CHD: HR 1.29 (95%-CI: 1.02–1.63) with 286 cases with a significant increase in CHD events of 29% in the CEE+MPA relative to placebo group (37 vs 30 per 10,000 person-years). The increase was in nonfatal MI with no significant differences observed in CHD deaths.<br>HR was 0.91 (95%-CI: 0.75–1.12) with 376 cases equivalent |

| Clinical trial | Outcomes assessed | Inclusion criteria | Intervention | Main findings                                                                                                                                                                                                                                                                                                            |
|----------------|-------------------|--------------------|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                |                   |                    |              | to a non-significant 9% reduction in CHD rates in the CEE group compared with placebo (49 vs 54 per 10,000 person-years).                                                                                                                                                                                                |
|                |                   |                    |              | 3. Stroke: The incidence in stroke was increased by 39% in CEE alone: HR: 1.39 (95%-CI: 1.10–1.77) with 276 cases with an absolute excess risk of 12 additional strokes per 10,000 person-years. Non-fatal stroke rates were higher in women receiving CEE+MPA (41% increase: 29 vs 21 per 10,000 person-years).         |
|                |                   |                    |              | 4. PE/VTE: Women in the CEE+MPA group had 2-fold greater rates of PE, HR 2.13 (95%-CI: 1.39–3.25) with 101 cases. Rates of VTE were 34 and 16 per 10,000 person-years in the CEE +MPA and placebo groups, respectively. In the CEE alone only the risk of DVT was statistically significant increased. not in VTE or PE. |
|                |                   |                    |              | 5. Bones: CEE+MPA group had a significantly lower incidence of hip fractures (10 per 10,000 person-years vs 15 per 10,000 person-years). CEE+MPA reduced the observed hip and clinical vertebral fracture rates by                                                                                                       |

| Clinical trial                                                         | Outcomes assessed                                                                                                                                                                                                    | Inclusion criteria | Intervention                                      | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|---------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                        |                                                                                                                                                                                                                      |                    |                                                   | one third.<br>Reductions in other osteoporotic fractures was 23% and total fractures 24% decrease. CEE group had a reduction in hip fracture rates (11 vs 17 per 10,000 person-years), clinical vertebral fractures (11 vs 17 per 10,000 person-years,) and total osteoporotic fractures (139 vs 195 per 10,000 person-years).<br>6. Cancer: No differences were observed in the rates of colorectal or total cancer incidents except colorectal cancer rates were significantly reduced by 37% in CEE+MPA.                                                             |
| <b>Women's Health Initiative Memory study (WHIMS)</b><br>Shumaker, [3] | To assess the role of CEE alone and combined CEE +MPA on 1) the incidence of probable dementia (primary outcome) and 2) mild cognitive decline (MCI) (secondary outcome) in older postmenopausal (aged 65–79) women. | See WHI above.     | Data from the combined WHI trials. See WHI above. | N=47 were diagnosed with probable dementia in the CEE-trial; N=28 among women assigned to CEE and N=19 in the placebo group. During follow-up, the “49% higher” incidence in women assigned to CEE relative to placebo (37 vs 25 per 10,000 person-years) was not statistically significant. In the CEE+MPA trial, the incidence was similar (45 vs 22 per 10,000 person-years). The HR associated with active treatment with CEE alone and CEE+MPA did not differ significantly even though the HR in the estrogen-alone trial was non-significant. When analyses were |

| Clinical trial                                                                               | Outcomes assessed                                                                                                                                                                                                                                                                                                                                                                             | Inclusion criteria                                                                                                                                                                                                                                                                                                             | Intervention                                                                                                                         | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
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|                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                |                                                                                                                                      | limited to data six months after first assessed nonadherence, the HR for probable dementia associated with CEE alone was 1.55 (95%-CI: 0.49–4.88).                                                                                                                                                                                                                                                                                                                                    |
| <b>The Women's Health Initiative Study of Cognitive Aging (WHISCA)</b><br>Resnick et al. [4] | To assess the efficacy of postmenopausal HRT on age related changes in specific cognitive functions including memory, cognition (measured by language, attention, spatial ability), motor function and mood.                                                                                                                                                                                  | N=2,302 postmenopausal women aged 66-84years (mean 73.9).                                                                                                                                                                                                                                                                      | See WHI above.                                                                                                                       | Women assigned to CEE+MPA had a negative impact on verbal memory over time and a trend toward a positive influence on figural memory relative to placebo after long-term therapy (average 4-5 years) with no significant differences in positive affect, negative affect or self-reported depressive symptoms. CEE-alone was associated with lower spatial rotational ability relative to placebo at the initial assessment, however this diminished over time.                       |
| <b>The Heart and Estrogen/progestin Replacement Study (HERS)</b><br>Grady et al. [5]         | Efficacy and safety of CEE+MPA treatment for secondary prevention of CHD in postmenopausal women.<br>Primary outcome: CHD events (nonfatal MI or CHD death).<br>Secondary cardiovascular outcomes: coronary artery bypass surgery, percutaneous coronary revascularization, hospitalization for unstable 2 angina, resuscitated cardiac arrest, congestive heart failure, stroke or transient | N=2,763 postmenopausal women with intact uterus.<br>Age: 44-79 years of age (mean age 66 years).<br>Prior history: $\geq 1$ CVD event(s); MI, coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, or other mechanical revascularization or $\geq 50\%$ occlusion of a major coronary artery. | 4-year RCT.<br>(1) 0.625 mg CEE +2.5mg MPA daily (N=1,380);<br>(2) placebo (N=1,383).<br>Adherence: 79% in year 1 and 70% by year 3. | Primary and secondary cardiovascular outcomes: No statistically significant differences between the randomized groups.<br>Among women who stopped taking HERS medication, risk of primary CHD events was elevated in the first month after stopping; however, no differences were observed between the HRT therapy and placebo group.<br>Secondary outcomes: No differences in total mortality, rates of breast, endometrial or other cancers or other fractures in the hormone group |

| Clinical trial                     | Outcomes assessed                                                                                                                                                          | Inclusion criteria                                   | Intervention                                                                                                                                                                                                                                                                                                               | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                    | ischemic attack and peripheral arterial disease.                                                                                                                           |                                                      |                                                                                                                                                                                                                                                                                                                            | relative to the placebo group. Increased risk of VTE (34 vs 12), DVT (25 vs 8) and PE (11 vs 4) in the hormone group relative to placebo, which authors suggest may be due to high age and multiple risk factors among HERS participants. LDL-C was significantly reduced by 14% and 3% in the placebo group. HDL increased by 8% and decreased by 2% relative to baseline in the hormone and placebo group respectively.                                                                                                                                                                                                                                                                                                       |
| <b>HERS II</b><br>Grady et al. [6] | To determine if the risk reduction observed in the later years of HERS persisted and resulted in an overall reduced risk of CHD events with additional years of follow-up. | N=2,321 of the 2,763 women who participated in HERS. | 6.8 years: 4.1-year RCT (HERS) and subsequent unblinded follow-up of 2.7 years (HERS II).<br>Was planned for 4-year follow-up but was terminated at the second annual review as the benefit in the group randomized to hormones relative to placebo were too low.<br>Adherence declined to 45% during year 6 of follow-up. | The lower rates of CHD events among women in the hormone group in the final years of HERS did not persist during the additional years of follow-up in HERS II. The HR for CHD events in the hormone group was higher in the first year of treatment however lower in the fourth year implying a decrease in risk during years 3-5 however no statistically significant trend over time. Analyses adjusted for potential confounders (incl. age, ethnicity, smoking, BMI, diabetes, systolic blood pressure, creatinine clearance, exercise, history of congestive heart failure and MI, baseline use of aspirin, ACE- inhibitors and statins, and statin use during follow-up plus adherence >80%) did not alter these results. |

| Clinical trial                                                  | Outcomes assessed                                                                                      | Inclusion criteria                                                                           | Intervention                                                                                                  | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                 |                                                                                                        |                                                                                              |                                                                                                               | It was examined whether the early increased risk in CHD events was limited to women at particularly high risk for events (age, prior manifestations of CHD, CHD risk factors, medication use); however, no clear evidence found that the early risk was limited to specific subgroups.                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Ancillary study of the HERS</b><br>Simon et al. [7]          | Risk of stroke among the participants enrolled in HERS.                                                | See HERS above.                                                                              | See HERS above.                                                                                               | 149 women (5%) had one or more strokes resulting in 26 deaths. 85% were ischemic; 8% were hemorrhagic strokes, and 6% were not classified. 139 nonfatal strokes and 26 fatal strokes occurred over a mean follow-up of 4.1 years. The incidence rates of any stroke event were 15/1,000 person-years among women assigned to combined HRT and 12/1,000 person-years among women assigned to placebo. Thus, CEE +MPA therapy was not significantly associated with risk of nonfatal stroke (HR 1.18; 95%-CI: 0.83–1.66), fatal stroke (HR 1.61; 95%-CI: 0.73–3.55), or transient ischemic attack (HR 0.90; 95%-CI 0.57–1.42) compared to placebo in postmenopausal women with cardiovascular disease. |
| <b>Women’s Estrogen for Stroke Trial</b><br>Viscoli et al. [51] | To examine the role of HRT for secondary prevention of CHD. Primary outcome: fatal or nonfatal stroke. | N=664 postmenopausal women with cerebrovascular disease who had suffered a recent (<90 days) | 2.8-year RCT. (1) 17 $\beta$ -estradiol (N=337) 1 mg/d; (2) placebo (N=327). When a nonfatal stroke occurred, | A total of 89 deaths and 103 nonfatal strokes occurred during the trial. There was no significant difference in incidence of deaths and nonfatal                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

| Clinical trial                                                                   | Outcomes assessed                                                                                                                                                                                                                                                                                                                                                   | Inclusion criteria                                                                            | Intervention                                                                                                                                                                                              | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                  | Secondary outcome: ischemic stroke or transient cerebral ischemia or nonfatal myocardial infarction (MI).                                                                                                                                                                                                                                                           | ischemic stroke or transient ischemic attack.<br>Age: 46–91 years of age (mean age 71 years). | the study drug was stopped and follow-up ended. Stroke followed by death within 30 days was classified as a fatal stroke. Mean follow-up was 33 ± 17 months with a minimum follow-up of 12 months.        | stroke, transient cerebral ischemia or nonfatal MI between women assigned to estrogen relative to placebo meaning HRT is ineffective as secondary CHD prevention in older postmenopausal women suffering recent cerebrovascular disease. The study found an increase in the risk of stroke early after E2 initiation; however, this was not statistically significant in women adherent to study medication. Furthermore, there were no differences in rates of VTE, breast cancer or hospitalization for fractures among the two groups.                                                                                     |
| <b>The Postmenopausal Estrogen/ Progestin Intervention (PEPI)</b><br>Miller, [9] | To assess HRT on selected cardiovascular risk factors in healthy, young postmenopausal women.<br>Primary outcomes:<br>- HDL-C<br>- systolic blood pressure<br>- serum insulin<br>- fibrinogen<br>Secondary outcomes:<br>- waist-hip ratio<br>- endometrial hyperplasia and cancer<br>- hysterectomies<br>- breast cancer and other cancers<br>- CVD events<br>- VTE | N=875 healthy young postmenopausal women.<br>Age: 45-64 years (mean age 56 years).            | 3-year RCT.<br>(1) placebo;<br>(2) CEE 0.625 mg/d<br>(3) CEE 0.625 mg/d + MPA 10 mg/d, days 1–12;<br>(4) CEE 0.625 mg/d + MPA 2.5 mg/d<br>(5) CEE 0.625 mg/d + MP 200 mg/d, days 1–12.<br>Adherence: 97%. | Women randomly assigned to any active treatment group had a significant increase in HDL-C relative to placebo. Average increases in HDL-C were similar in the CEE (5.6 mg/dl) and CEE + MP (4.1 mg/dl) group and significantly higher than observed in the CEE + cyclic or continuous MPA groups (1.6 mg/dl and 1.2 mg/dl respectively). LDL-C decreased comparably across all active treatment groups by an average of 15.9 mg/dl across, significantly different from placebo. Triglycerides increased comparably and significantly in all active treatment groups (mean increase to 111 mg/dl from 98.3 mg/dl) relative to |

| Clinical trial                                                                                                                                 | Outcomes assessed                                                                                                                                | Inclusion criteria                                                                                                                                 | Intervention                                                                                                                             | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                |                                                                                                                                                  |                                                                                                                                                    |                                                                                                                                          | placebo. No significant differences were observed in systolic blood pressure and serum insulin levels however fasting glucose levels decreased significantly in all active treatment groups. Women assigned to placebo had greater increases in fibrinogen relative to women assigned to active treatment (0.10 g/L vs -0.02–0.06 d/L respectively).                                                                                                                                                                                                                                         |
| <b>The Postmenopausal Estrogen/ Progestin Intervention (PEPI) regarding bone mineral density</b><br>The Writing Group for the PEPI Trial, [10] | To assess the effects of HRT on BMD at the spine and hip in postmenopausal women.<br>Primary outcome: BMD at baseline, 12 months, and 36 months. | See PEPI above.                                                                                                                                    | See PEPI above.                                                                                                                          | Women assigned to placebo lost an average of 1.8% of spine BMD and 1.7% of hip BMD by 36-months. Women assigned to active regimens gained BMD at both sites; ranging 3.5% to 5.0% mean total increases in spinal BMD and a mean total increase of 1.7% of BMD in the hip. Changes in BMD were significantly greater in women assigned to active treatment relative to placebo. Older women, women with low initial BMD, and those with no previous hormone use gained significantly more bone than younger women, women with higher initial BMD, and those who had used hormones previously. |
| <b>Kronos Early Estrogen Prevention Trial (KEEPS)</b><br>Miller et al. [11]                                                                    | The effects of HRT in recently postmenopausal women.<br>Primary outcome: Progression of subclinical atherosclerosis (measured by carotid artery  | N=727 healthy (free of subclinical CVD).<br>Recent menopause: within 6 months-3 years of natural menopause (mean of 1.4 years).<br>Age 42-58 years | 4-year RCT<br>(1) o-CEE 0.45 mg/d (N=230);<br>(2) t-E2 50 µg/d (N=222);<br>(3) placebo (N=275).<br>All groups received cyclic 200 mg MP/ | 1. CIMT increased similarly across all three groups (0.007 mm/y after 48 months).<br>2. There was a non-significant trend for reduced accumulation of CAC with o-CEE                                                                                                                                                                                                                                                                                                                                                                                                                         |

| Clinical trial                                                            | Outcomes assessed                                                                                                                 | Inclusion criteria                                 | Intervention                                                                               | Main findings                                                                                                                                                                                                                                                                                                                                                                                       |
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|                                                                           | intima-media thickness, CIMT). Secondary outcomes: Other risk factors for cardiovascular disease (LDL-C, HDL-C, CAC).             | (mean of 52.6 years).                              | day 12 days/ month.                                                                        | and t-E2 relative to placebo.<br>3. No significant changes in blood pressure across groups.<br>4. No severe adverse effects including venous thrombosis.<br>5. Other benefits found in both active treatment groups include significantly improved sleep (measured as sleep satisfaction and sleep latency, sleep disturbances only improved by t-E2) and maintenance of BMD compared with placebo. |
| <b>KEEPS ancillary menopausal symptoms study</b><br>Santoro et al. [12]   | Assessing menopausal symptoms at 6, 12, 24, 36, and 48 months post-randomization.                                                 | See KEEPS above.                                   | See KEEPS above.                                                                           | Both o-CEE and t-E2 treatment significantly reduced hot flashes (44% at baseline to 28.3% placebo; 7.4% t-E2; 4.2% o-CEE) and night sweats (35% at baseline to 19% placebo, 5.3% for t-E2; 4.7% for o-CEE) after six months with no significant difference between active treatment arms.                                                                                                           |
| <b>KEEPS ancillary sexual function study</b><br>Taylor et al. [13]        | Assessing sexual function measured by the Female Sexual Function Inventory (FSFI) questionnaire.                                  | N=670 of the 727 who participated in KEEPS.        | See KEEPS above.                                                                           | Treatment with t-E2 improved FSFI overall score relative to placebo, however in the individual domains of sexual function both t-E2 and o-CEE differed significantly compared with placebo.                                                                                                                                                                                                         |
| <b>KEEPS ancillary cognition study (KEEPS-Cog)</b><br>Gleason et al. [14] | Whether HRT in recently postmenopausal women modifies risk of Alzheimer's Disease (AD). Primary outcomes:<br>1. Mini Mental State | N=693 of the 727 women that participated in KEEPS. | Avg. follow-up period: 2.85 years for cognitive outcomes and 2.76 years for mood outcomes. | 1. Aβ deposition was lower in women assigned to t-E2 therapy relative to placebo. Not among women assigned to o-CEE. Stratifying women by APOEε4 genotype, it was                                                                                                                                                                                                                                   |

| Clinical trial                                                                                  | Outcomes assessed                                                                                                                                                                                                                   | Inclusion criteria                                                                                                                                                                                                      | Intervention                                                                                                                                             | Main findings                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                 | Examination (MMSE).<br>2. Four cognitive factors: verbal learning/ memory, auditory attention/ working memory, visual attention/ executive function and speeded language/mental flexibility<br>3. Mood: The Profile of Mood States. |                                                                                                                                                                                                                         |                                                                                                                                                          | found that the reduced A $\beta$ deposition in the t-E2 group was particularly among APOE $\epsilon$ 4 allele carriers, who are known to be at increased risk of AD.<br>2. For mood, model estimates found that women treated with o-CEE had fewer symptoms of depression and anxiety compared to women on placebo. Mood outcomes for women randomized to t-E2 were similar to those for women on placebo. |
| <b>KEEPS ancillary skin study</b><br>Owen et al. [15]                                           | Examined effects of HRT on wrinkles (assessed on the face and neck) and skin rigidity (assessed in forehead and cheek) in postmenopausal women.                                                                                     | N=116 of the 727 who participated in KEEPS.                                                                                                                                                                             | See KEEPS above.                                                                                                                                         | Neither total wrinkle score nor total rigidity score was significantly different at baseline or over the 4-year follow-up among patients randomized to CEE, E2, or placebo. Skin wrinkle and rigidity scores were primarily affected by race/ ethnicity.                                                                                                                                                   |
| <b>ELITE (The Early vs Late Intervention Trial with Estradiol (ELITE))</b><br>Hodis et al. [16] | To examine “the timing hypothesis” on the risk of CVD. Primary outcome: The rate of change in CIMT measured 6-monthly during trial. Secondary outcomes: Measures of CAC measured by cardiac-CT.                                     | N=642 healthy, postmenopausal women stratified in:<br>1) Early menopause <6 years (avg 3.5 yrs, median age 55.4 years old).<br>2) Late menopause >10 years after menopause (avg 14.3 years, median age 65.4 years old). | 5-year RCT.<br>(1) Oral 17 $\beta$ -estradiol 1 mg/d;<br>(2) placebo<br>Women with intact uterus: + cyclic MP vaginal gel or placebo.<br>Adherence: 98%. | After 5-year intervention: rate of CIMT progression was significantly lower in the early menopause group (-0.0044 mm/year) among women assigned to estradiol relative to placebo (-0.0078 mm/year). In the late menopause group CIMT progression didn't differ significantly among groups (-0.0100 mm/year vs -0.0088 mm/year respectively). Findings were similar when adjusting for 80%                  |

| Clinical trial                                                                   | Outcomes assessed                                                                                                                                                                                                                                                                                                          | Inclusion criteria                                                                    | Intervention                                                                                                                   | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                                                  |                                                                                                                                                                                                                                                                                                                            |                                                                                       |                                                                                                                                | <p>adherence as adherence rate was high (mean 98% across groups). Findings were independent of hysterectomy status and use of MP. The effect of HRT was significantly lower in the early vs late postmenopausal group assessing the absolute value of CIMT after the 5-year intervention. The CT measurements of CAC, total stenosis, and plaque didn't differ between the estradiol and placebo groups within either postmenopausal stratum.</p>                                    |
| <b>ELITE-Cog</b><br>Henderson et al. [17]                                        | Effects of HRT on cognitive abilities. Primary outcome: change in verbal episodic memory assessed at 2.5 and 5 years and compared between treatment groups measured by standardized composite of neuropsychological test scores. Secondary outcomes: executive functions and global cognition measured by cognitive tests. | N=567 after 2.5 years.<br>N=455 after 5 years.                                        | See ELITE above.                                                                                                               | For verbal memory, the mean estradiol minus placebo standardized difference in composite scores (HR -0.06; 95%-CI: -0.22-0.09) was not significant. Differences were similar in early and late postmenopause groups. Interactions between postmenopause groups and differences between treatment groups were not significant for executive functions or global cognition. Meaning estradiol neither benefits nor harms these cognitive abilities regardless of time since menopause. |
| <b>The Danish Osteoporosis Prevention Study (DOPS)</b><br>Schierbeck et al. [18] | To examine the long-term effects of HRT in healthy, recently postmenopausal women. Primary outcomes: 1. mortality                                                                                                                                                                                                          | N=1,006 healthy, recently postmenopausal women. Age: 45-58 years (median 49.7 years). | 10.1-year RCT and subsequent unblinded follow-up for 5.7 years. 15.8 years overall. After a mean duration of 10.1 years, women | 16 women in the treatment group suffered from primary composite endpoint compared to 33 in the control group (HR 0.48, 95%-CI: 0.26-0.87) and 15 died                                                                                                                                                                                                                                                                                                                                |

| Clinical trial                              | Outcomes assessed                                                                                                                                                                                                                                                                  | Inclusion criteria                                              | Intervention                                                                                                                                                                                                                                                                                                                                 | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                             | 2. admission to hospital, myocardial infarction, or heart failure.<br>Secondary outcomes: admission to hospital for stroke.<br>Safety endpoints: 1. death, 2. diagnosis of breast cancer or other cancer, 3. admission to hospital for pulmonary embolism or deep vein thrombosis. |                                                                 | randomized to treatment were encouraged to discontinue HRT August 1st, 2002, following adverse outcomes in the WHI.<br>1) 2 mg 17 $\beta$ -estradiol/d (hysterectomy);<br>2) 2 mg 17 $\beta$ -estradiol/d 12 d/month, 2 mg estradiol/d + 1 mg NETA for 10 d/month and 1mg 17 $\beta$ -estradiol/d 6 days/month (intact uterus)<br>3) placebo | relative to 26 (HR 0.57, 95%-CI: 0.30–1.08). After 16 years of total follow-up, the reduction in the primary endpoint was still present. Fewer women died relative to placebo however this was not significant (HR 0.66, 95%-CI: 0.41–1.08). There was no apparent increase in risk of cancer (any cancer incidence: 36 in treated group vs 39 in control group, HR 0.92; 95%-CI: 0.58–1.45; breast cancer: 10 in treated group vs 17 in control group, HR 0.58; 95%-CI: 0.27–1.27), VTE (HR (2 in treated group vs 1 in control group) was 2.01 (95%-CI: 0.18–22.16)), or stroke (HR 11 in treated group vs 14 in control group) was 0.77 (95%-CI: 0.35–1.70). Younger women (<50 years) receiving HRT had a significantly reduced risk of breast cancer relative to control group (HR 0.49, 95%-CI 0.28–0.87) and women undergoing hysterectomy (N=192) receiving estrogen alone (HR 0.42, 95%-CI 0.18–0.97). There were no statistically significant differences in stroke rates, rates of DVT or PE. The incidents were generally low (9 in HRT-group and 4 in placebo respectively). |
| <b>DOPS, bones</b><br>Mosekilde et al. [19] | To assess whether HRT in recently postmenopausal women can be used as primary                                                                                                                                                                                                      | N=2,016 healthy women.<br>Age: 45-58 years (median 50.8 years). | See DOPS above. The study was originally two-folded:<br>1) a randomized                                                                                                                                                                                                                                                                      | Risk of forearm fracture was significantly reduced (HR 0.45, 95%-CI 0.22–0.90) in women                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

| Clinical trial                                              | Outcomes assessed                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Inclusion criteria                                                                                                                                                              | Intervention                                                                                                                                                | Main findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|                                                             | prevention of fractures.<br>Primary outcomes: BMD at the lumbar spine (L2-L4), the femoral neck and the forearm at inclusion, after 6 months, 1, 2, 3 and 5 years. X-rays of the spine (Th4 and L5) at inclusion and after 5 years.                                                                                                                                                                                                                               |                                                                                                                                                                                 | arm, randomized to HRT (N=502) and placebo (N=504)<br>2) a non-randomized arm, assigned to HRT (N=221) and no HRT (N=789).                                  | assigned to active treatment with HRT. Restricting the analysis to women who adhered to their initially assigned group of wither HRT (N=395) or placebo/no HRT (N=977), there was a significant reduction in overall risk of fracture (HR 0.61, 95%-CI 0.39–0.97) and the risk of forearm fractures (HR 0.24, 95%-CI 0.09–0.69).                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>REPLENISH</b><br>Liu et al. [52];<br>Kaunitz et al. [53] | To assess the efficacy and safety of a combined 17- $\beta$ -estradiol and natural progesterone capsule in various doses vs placebo for reducing the frequency and severity of moderate to severe menopause related VMS in postmenopausal women and to evaluate endometrial safety. Primary outcomes: mean change in frequency of moderate to severe VMS. Safety endpoints: endometrial hyperplasia and changes from baseline breast examinations and mammograms. | N=1,825 healthy postmenopausal women with intact uterus who are seeking treatment for menopause-related VMS. Age: 40-65 years (mean age 55). Mean time since menopause 6 years. | 1-year RCT. Four combinations of estradiol/ progesterone:<br>(1) 1.0 mg/100 mg<br>(2) 0.5 mg/100 mg<br>(3) 0.5 mg/50 mg<br>(4) 0.25 mg/50 mg<br>Or placebo. | For women who received the E2/P4 1/100 or 0.5/100 dose, ~80% had at least a 50% decrease and 68% and 58%, respectively, had at least a 75% decrease in their moderate to severe VMS, all of which were significantly greater than with placebo. After 12 weeks of treatment, women who received the 1/100 dose or the 0.5/100 dose had 3 days in mean per week with no moderate to severe VMS and 56% and 47%, respectively, of the women no longer had any severe VMS. The incidence of endometrial hyperplasia or malignancy was 0% with all four doses and placebo after 12 months. No increasing incidence of abnormal mammograms after one year of treatment (all but 8 (0.4%) mammograms at screening were normal). |

**Table A1.**  
*A summary of the clinical trials examining the benefits and risks of HRT on age-related diseases in postmenopausal women.*

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# Hormone Replacement Therapy: Is It Always Necessary in Natural and Surgical Menopause?

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## Abstract

The aim of this paper is to delve into the multifaceted effects of hormone replacement therapy (HRT) in postmenopausal women, elucidating its therapeutic benefits and potential risks. HRT demonstrates efficacy in alleviating genitourinary and vasomotor symptoms, enhancing sleep, mitigating myalgias, addressing skin issues, bolstering emotional well-being, improving joint health, and enhancing overall quality of life. Moreover, HRT exerts a positive influence on bone density, thereby reducing the incidence of osteoporotic fractures. However, we also scrutinize the associated risks, including heightened susceptibility to cardiovascular disease, breast cancer, ovarian cancer, and thromboembolic events. The administration method and dosage of hormones emerge as pivotal factors in modulating these risks. Furthermore, we explore the impact of genetic factors on thromboembolic events in women undergoing oral estrogen therapy. Additionally, considerations regarding the duration of HRT treatment are discussed, with annual reassessment advocated, albeit lacking consensus on optimal treatment duration. We also examine the implications of oophorectomy, delineating potential hormonal dysfunction post-hysterectomy and its ramifications. Moreover, we investigate the cardiovascular and lipid profile effects of ovarian conservation post-hysterectomy, suggesting potential advantages over oophorectomy. In conclusion, this is a comprehensive overview of both the benefits and risks entailed in HRT utilization among postmenopausal women, thereby facilitating informed decision-making in clinical practice.

**Keywords:** menopause, hormone replacement therapy, natural menopause, surgical menopause, effects of hormone replacement therapy

## 1. Introduction

In 2030, as per projections from the World Health Organization, the number of women aged 50 years and above is anticipated to exceed 1.5 billion. Although a woman's menopausal period is characterized by a lack of estrogen, it is expected that her healthy and productive life will continue for at least another 30 years [1, 2]. The large and constantly growing population of peri- and post-menopausal women has contributed to the fact that the treatment of menopause-related symptoms and disorders is an important socio-economic and scientific parameter in industrialized countries with a perspective of its development in developing countries as well [1, 2]. The primary reasons for implementing this treatment include addressing vasomotor symptoms, complications arising from the atrophy of the genitourinary system, preventing osteoporosis and cardiovascular diseases, and managing ovarian failure in women of reproductive age, presenting as early menopause, and menopause. Contraindications include a history of breast cancer, ovarian cancer, or uterine cancer, as well as a history of thromboembolic events, untreated high blood pressure, liver disease, and pregnancy or the desire to become pregnant. Similar to any medication, hormone replacement therapy (HRT) has the potential to induce side effects. However, these side effects typically subside within 3 months of initiating the treatment. Common side effects include breast tenderness, headaches, malaise, abdominal pain, and vaginal bleeding [1, 2].

## 2. Effects of hormone replacement therapy

Hormone replacement therapy (HRT) continues to be the most effective therapeutic approach for addressing genitourinary symptoms in postmenopausal women, and it is also highly effective in managing vasomotor symptoms [3, 4]. At the same time, it has a beneficial effect and improves other types of disorders related to menopause, such as sleep disorders, myalgias, skin problems, emotional disorders, and joint disorders, and also improves the quality of life of patients but also their sexual issues (Tables 1 and 2) [3, 4]. Furthermore, the beneficial effects of HRT include the

| Symptoms of menopause          | Frequency | Rate |
|--------------------------------|-----------|------|
| Hot flashes, sweating          | 90        | 81.9 |
| Discomfort                     | 77.7      | 70.0 |
| Sleep problems                 | 80        | 72.7 |
| Depressed mood                 | 56        | 50.9 |
| Irritability                   | 76        | 69.1 |
| Anxiety                        | 70        | 63.6 |
| Physical and mental exhaustion | 94        | 85.4 |
| Sexual problems                | 74        | 67.3 |
| Bladder Problems               | 48        | 43.6 |
| Gulf dryness                   | 46        | 41.8 |
| Joint and muscle discomfort    | 94        | 85.4 |

**Table 1.**  
*Frequency and rates of occurrence of menopausal symptoms among participants [3].*

|              |                                                                                            |
|--------------|--------------------------------------------------------------------------------------------|
| Hypothalamic | Hot flashes<br>Palpitations convulsions<br>Tingling sensation                              |
| Psychogenic  | Nervousness headaches<br>Change of sexuality<br>Insomnias                                  |
| Metabolic    | Increased blood lipids osteoporosis<br>Myalgias urinary incontinence<br>Atrophic vaginitis |

**Table 2.**  
*The clinical manifestations of menopause can be summarized in three categories based on their etiology: (a) hypothalamic, (b) psychogenic and (c) metabolic origin [4].*

reduction of the incidence rate of colon cancer [5], diabetes mellitus, insulin resistance [3], as well as lipids and metabolic syndrome, with the oral administration of preparations. Nevertheless, one drawback of this method is the potential elevation of blood pressure. Despite this, it is not a contraindication for administration, as blood pressure is typically regulated prior to the initial treatment. As reported by Palacios et al. [6], there is a positive response from some progestogens in improving blood pressure, while Henderson [7] reports that there is a positive effect of HRT, at the onset of menopause, and on cognitive function, although it is an issue that remains to be investigated. However, when there is a pre-existing cognitive impairment in older women, then the effect of HRT ceases to be beneficial and instead may worsen the condition [7, 8]. At the same time, it has been reported by some researchers that the administration of HRT at the onset of menopause may reduce the incidence of Alzheimer's disease [8].

**2.1 Postmenopausal osteoporosis**

The positive effect of HRT in postmenopausal women in preventing bone loss has already been reported, as it reduces the rate of osteoporotic fractures, as well as the rate of spine and hip fractures, in patients who may be at low risk [9]. It also improves the bone density of postmenopausal women, even with small amounts of estrogen [10], which is why HRT is the main choice for the prevention of osteoporosis in postmenopausal women who experience more fractures and belong to the age range over 60 years. The same is true for women who experience menopause at a younger age [3]. However, when treatment is stopped, the protection in terms of bone density also stops, although it has been reported that some degree of protection still remains. Also, there is no reason to start HRT treatment in women over 60 simply to prevent fractures. HRT has long been known to significantly increase bone mineral density (BMD). In a meta-analysis of 57 trials (prevention and treatment trials) involving approximately 10,000 women, the combined results suggested that, on average, the change in BMD was significantly higher in the HRT group (both unopposed and unopposed estrogen) across all measurements. After 1 year, the HRT group showed an average increase in lumbar spine BMD of 5.4%, while the forearm and femoral neck also increased by 3.0% and 2.5%, respectively. After 2 years of treatment, the percentage change in favor of HRT increased by approximately 1.5% in all regions with increases of 6.8%, 4.5%, and 4.1% in the lumbar spine, forearm, and the femoral neck, respectively [11, 12]. HRT is also effective in preventing osteoporotic fractures.

In a meta-analysis of 22 randomized trials, there was an overall 27% reduction favoring the HRT groups in nonvertebral fractures in a pooled analysis (RR = 0.73, 95% CI, 0.56–0.94,  $P = 0.02$ ). Only for hip and wrist fractures did the effectiveness of HRT appear more impressive (RR = 0.60, 95% CI, 0.40–0.91,  $P = 0.02$ ) [13]. In a randomized trial investigating the effects of tibolone on fractures, 254,538 women at risk of fracture were assigned to a placebo or tibolone group. Over a median treatment duration of 34 months, compared with the placebo group, vertebral fractures were 45% lower in the tibolone group, (RR = 0.55, 95% CI, 0.41 to 0.74,  $P < 0.001$ ) and the nonvertebral fracture was reduced by 26% (RR = 0.74, 95% CI, 0.58 to 0.93,  $P = 0.01$ ) [14]. It is worth noting that estrogen withdrawal leads to rapid bone loss, and within a year most of the previously increased BMD accumulated over 3–4 years is gone. In a randomized study, which included early postmenopausal women aged 55 years, HRT increased BMD by 5–6%. However, 4 years after stopping treatment there was a rapid decline in spine BMD of 7% in the HRT group. Another similar analysis showed that within 2 years hip fractures increased by 50% and after 5 years by 77%. It is therefore recommended that women who stop HRT choose other treatments to prevent osteoporosis [15]. However, it should be emphasized that estrogen is not considered a first-line option for fracture prevention [16–18].

## **2.2 Coronary artery disease**

In postmenopausal women, cardiovascular disease stands as the predominant cause of morbidity and mortality, as indicated by a WHO study. This study revealed that participants administered a combination of estrogen and progesterone exhibited a heightened risk of coronary heart disease (HR 1.29). Further analysis suggested that patient age at the initiation of hormone replacement therapy (HRT) and the duration since menopause played a role in this outcome [19]. According to Hodis [20], findings from studies such as those conducted by the Women's Health Initiative (WHI) or the Nurses' Health Study, along with a meta-analysis of 23 studies, indicated that administering either estrogen combined with progesterone or estrogen alone to women aged 50–59 reduced the likelihood of developing coronary heart disease. Similar observations were made in women under the age of 60, where the administration of raloxifene yielded comparable results [21]. Also, administration of estrogens reduced the incidence of coronary artery calcification in hysterectomized women aged 50–59 years who were screened by cardiac computed tomography [22]. Contrarily, adverse outcomes emerge when hormone replacement therapy (HRT) is administered 10–20 years post-menopause, particularly in women with pre-existing endothelial atherosclerosis, as it escalates the risk of coronary heart disease [23]. Postmenopausal women who already suffer from coronary heart disease and are older also face heightened concerns, while the beneficial effect of HRT is possible for most women who have a healthy endothelium, and are close to menopause, and are protected from cardiovascular diseases [23].

## **2.3 Breast cancer**

While the specific causes of breast cancer remain unknown, certain predisposing factors include a sedentary lifestyle, obesity, and alcohol consumption. In assessing the relationship between breast cancer and hormone replacement therapy (HRT), it is crucial to consider and evaluate the risk rate in proportion to other predisposing factors [24]. As mentioned earlier, the administration of

estrogen combined with progesterone has been associated with an increased risk of breast cancer [5]. Data from the Collaborative Group on Hormonal Factors in Breast Cancer reveals insights from a meta-analysis of 51 studies, highlighting the significance of treatment duration [25]. The findings indicate that women initiating HRT for the first time do not face an elevated risk of breast cancer, whereas the risk is heightened in those who had received HRT in previous years [26]. Probably, as reported by Fournier et al. [27], the type of progesterone administered also plays a role, i.e., if natural progesterone or dydrogesterone is administered, then the risk is reduced, compared to synthetic progesterone. Other studies have shown that the duration of treatment plays a role. Postmenopausal women who had undergone hysterectomies and received estrogen-only therapy had no or little risk of breast cancer after several years of treatment. The findings from the World Health Organization (WHO) and the Nurses' Health Study indicate that the administration of estrogen for durations exceeding 7–15 years appears to carry a relatively small percentage of risk for breast cancer occurrence. Simultaneously, the WHO study revealed a slight reduction in risk [28, 29]. Notably, women with a history of hormone replacement therapy (HRT) demonstrated a significant reduction in risk. In the Collaborative Group on Hormonal Factors in Breast Cancer [30, 31] and Chen et al. [32] studies, it was observed that the incidence of breast cancer may increase after 5 years of treatment. However, the Nurses' Health Study notes that this risk may appear after a longer period (15–20 years) of treatment.

Concerning the incidence of breast cancer in women exhibiting dense breasts on mammography, there is an elevated risk. The use of hormone replacement therapy (HRT) has been associated with an increase in breast density; however, it has not been conclusively established that this group of women faces a higher risk of breast cancer [3].

Additionally, compared to women who were diagnosed with breast cancer but did not take HRT, there was a comparatively reduced death rate in cases where the cancer was discovered in women who were already on HRT. This phenomenon may be attributed to early diagnosis, systematic follow-up, or the possibility that tumors in HRT-receiving individuals are less aggressive or exhibit a better response to treatment [30].

Nevertheless, when hormone replacement therapy (HRT) treatment is discontinued, research conducted by the Collaborative Group on Hormonal Factors in Breast Cancer [25] and Chlebowski et al. [26] indicates a decrease in the risk of women developing breast cancer. It is crucial to note that the timeframe for the development of breast cancer is extended, with a pre-cancerous stage requiring 5–10 years to progress into cancer [5]. Published findings on the risk of breast cancer associated with different types of hormone replacement therapy (HRT) display inconsistencies, and there is limited information on the long-term effects. Both published and unpublished evidence on these correlations were assessed in a 2019 pooling of epidemiological data by the Collaborative Group on Hormonal Factors in Breast Cancer, with a focus on pertinent randomized data. The primary analyses utilized individual participant data from all eligible prospective studies that had solicited information regarding the type and timing of HRT use. The main analyses were based on individuals with complete data. Studies were identified through a systematic search of multiple formal and informal sources, covering the period from January 1, 1992 to January 1, 2018. Current users were included up to 5 years (with a mean of 1–4 years) after their last HRT use. Logistic regression was employed to derive adjusted risk ratios (RRs), comparing specific groups of HRT users to those who had never used HRT. The findings

showed that during follow-up, 108,647 postmenopausal women developed breast cancer at a mean age of 65 years (SD 7). A total of 55,575 (51%) had used HRT. Among women with complete data, the mean duration of HRT was 10 years (SD 6) in current users and 7 years (SD 6) in former users, and the mean age at menopause was 50 years (SD 5) and 50 years (SD 6) starting HRT (All forms of hormone replacement therapy (HRT), with the exception of vaginal estrogen, were linked to elevated risks of breast cancer. These risks showed a consistent rise with the duration of HRT use, and they were notably higher for preparations containing both estrogen and progestogen compared to those containing estrogen alone.

Among users, the risk was deemed excessive during the first 4 years, and it doubled in years 5–14. Specifically, during years 5–14, the consistent use of progestogen daily heightened the risk associated with estrogen-progestogen therapy, and this risk decreased when progestogen use was less frequent. For a specific HRT preparation, the risk ratios (RRs) during years 5–14 of current use were substantially higher for estrogen receptor-positive tumors compared to estrogen receptor-negative tumors. Moreover, these RRs were consistent across women initiating HRT at ages 40–44, 45–49, 50–54, and 55–59 years, but declined after age 60 or with the onset of menopausal symptoms (with a minor risk associated with estrogen-only HRT in women who were obese). After discontinuation of HRT, the excess risk persisted for more than 10 years. Its magnitude depends on the duration of previous use, with a slight excess after less than 1 year of HRT use [31]. According to the interpretation of the results, if these associations are primarily causal, then 5 years of hormone replacement therapy (HRT) starting at age 50 will increase the incidence of breast cancer in women of average weight in developed countries between the ages of 50 and 69. The estimated increases in breast cancer incidence are approximately one in 50 for daily users of estrogen-progestogen preparations, one in 70 for users of estrogen with intermittent progestogen preparations, and one in 200 for users of estrogen-only preparations. For a 10-year duration of HRT use, these excesses would be roughly twice as stated by the Collaborative Group on Hormonal Factors in Breast Cancer [31].

## **2.4 Ovarian cancer**

A large number of studies [5, 32, 33] report that women taking HRT have a high risk of developing ovarian cancer, just as the risk is high for women taking estrogen, but it is an issue that is still in question, as the conclusions remain conflicting [32].

## **2.5 Strokes**

Vascular strokes and the effect of HRT on them is an issue that is under study, regarding the rate of stroke, although studies so far have shown that most postmenopausal women are at high risk of having a stroke, a risk that decreases if the women's age is under 60 Writing Group on behalf of Workshop Consensus Group [31, 34]. As reported by Rossouw et al. [19], it has been observed in the WHI study that there was a high incidence of stroke in the entire population (HR 1.32), which was found to be reduced in the age group of 50–59 years. The Nurses' Health Study had the same result, which also found an increased risk of stroke, regardless of the age of the participants, while age was not an inhibitory factor for the subgroups of participants who received a small amount of doses estrogen and there was no increased risk of stroke in these women [35].

## **2.6 Thromboembolic events and pulmonary disease**

Among the adverse effects of HRT are thromboembolic events, in which the probability of occurrence increases when the age of women exceeds 60 years, the risk is additionally linked to obesity and oral intake of estrogen, as opposed to when administration is conducted transdermally, where the risk is significantly diminished [36–38]. For this reason, transdermal administration is recommended for postmenopausal women who are at risk of thromboembolic events due to a history of thromboembolic disease or increased body weight. It is also pointed out that thromboembolic events also depend on the progesterone administered [37]. According to studies, thromboembolic events depend on genetic factors and occur when oral estrogens are administered (e.g., factor V Leiden, some CYP3A5 polymorphisms, G20210A mutation in the prothrombin gene) [38, 39].

## **3. HRT precautions**

The hormone replacement therapy (HRT) formulations primarily consist of reproductive steroids, specifically estrogen, either in isolation (predominantly during the 1950s–1960s) or in conjunction with progestogens or androgens. The same category includes tibolone and phytoestrogens, while raloxifene is a non-steroidal substance [40, 41]. Estrogens are divided into two categories: natural and synthetic. Natural estrogens are mainly used in HRT preparations over synthetic estrogens due to fewer and less intense adverse effects, and this is because synthetics cause to a greater degree unwanted activation of liver enzymes. A special category is the conjugated estrogens derived from the urine of pregnant horses, with the main component estrone sulfate, secondary equilin sulfate, and 17 $\alpha$  dihydroequilin sulfate. Equilin has a strong effect and is stored in adipose tissue, so it sometimes continues to work even after treatment is stopped [41, 42]. The term progestogen refers to all steroids used as a substitute for endogenous progesterone. These HRT preparations contain mainly synthetic progestogens belonging to two chemical classes, progesterone derivatives and nor-testosterone derivatives. Drospirenone is a new progestogen derivative of 17 $\alpha$ spironolactone with antiandrogenic and antisaltocorticoid activity. In particular, progesterone derivatives include dihydroprogesterone, medroxyprogesterone acetate (MPA), chlormadinone acetate (CMA), cyproterone acetate (CPA) and medrogestone, and 19nor testosterone derivatives include norethisterone, norgestimate, levonorgestrel, Lynestrenol, Gestodenis, Desogestrel and Dienogest [39]. The desirable actions of progestogens include the preservation and support of the endometrium after estrogenic influence, the antimitotic effect on the endometrium, and possibly some positive psychotropic effect. On the contrary, the side effects include a mild androgenic effect (more evident in testosterone derivatives) manifested as hirsutism and disturbance of lipid metabolism. The 19nor testosterone derivatives selectively bind the progesterone receptors with which they have a high degree of affinity, thus allowing the administration of a lower dosage, but at the same time, they also bind the androgen receptors. Finally, dienogest combines the advantages of 19nor-progestogens (high oral bioavailability, strong progesterone effect on the endometrium) with the corresponding ones of progesterone derivatives (antiandrogenic and antimitotic effect, moderate antigonadotropic effect). It is also not bound by endogenous proteins (SHBG-CBG). Finally, a special form of progestogen is drospirenone, which exhibits antisaltocorticoid, antiglucocorticoid, and antiandrogenic effects. The

postmenopausal ovaries and adrenal glands are a source of androgen production. But with the passage of age, there is a drop in the level of circulating androgens by 50% with the greatest decrease (75%) concerning dehydroepiandrosterone (DHEA). On the contrary, at least 5 years must pass before the level of testosterone begins to fall. The combined administration of androgens and estrogens in postmenopausal patients is constantly gaining ground, especially in cases with previous oophorectomy.

The main advantages of the administration of androgens are the remission of vasomotor symptoms, the improvement of mental mood since androgens have a key role in the psychophysiology of women with significant interventions in (mental functions, emotions, and desire for sexual activity) as well as the improvement of sleep quality, the increased energy, and ability to deal with stress and the strong anabolic action.

Disadvantages of androgen administration include increased risk of cardiovascular disease (neutralization of potential beneficial effects of estrogen), reduction of HDL levels without substantial change in LDL counterparts, masculinization, and hirsutism (dose-dependent). A quite interesting substance with androgenic action is dehydroepiandrosterone and its divine derivative, which when administered causes a decrease in subcutaneous thickness and in general adipose tissue, an increase in muscle mass, and a decrease in plasma glucose levels. In addition, the presence of antimutagenic activity has been established in experimental animals [43, 44].

Tibolone is a synthetic steroid derivative of 19-nor testosterone that exhibits simultaneous estrogenic, progestogenic, and androgenic effects. The degree of affinity for estrogens is small for tibolone as a whole and for the 3a and 3b hydroxy isomers, for progesterone and androgens, it is small for tibolone as a whole, moderate for the  $\Delta 4$  isomer while there is no chemical affinity for the 3a and 3b hydroxy isomers. The advantages of the method include the reduction of climacteric vasomotor symptoms and estrogenic effect on bone tissue, the compensation of estrogenic action in the endometrium, and the improvement of the desire for sexual intercourse. Its disadvantages include the fact that the degree of its effect on other tissues especially on the breast is not yet known. Tibolone is administered in a daily dose of 2.5 mg for the relief of symptoms and the control of uterine bleeding [44]. Raloxifene and bazedoxifene are classified as selective estrogen receptor modulators (SERMs). Their action is both agonistic and antagonistic to estrogen depending on the target tissue. In particular, it mimics the action of estrogen on bone tissue, the cardiovascular system, and lipid metabolism. This action is different from that of  $17\beta$  estradiol and tamoxifen. They exhibit anti-estrogenic activity in the endometrium and have an inhibitory binding effect on estrogen receptors, antagonizing the estrogen-dependent proliferation of MCF-7 cells in breast tumors. Their advantages include the absence of mitotic activity in the breast and endometrium. Other advantages are the fact that they can be administered without progestogen to women with an intact uterus and act satisfactorily in the prevention of osteoporosis. Finally, they do not affect ovarian estrogen production and the hypothalamic-pituitary axis. Their disadvantages include the unsatisfactory treatment of climacteric symptoms and the occurrence of adverse effects such as hot flashes and leg cramps. In light of the aforementioned, they are the recommended course of action for preventing osteoporosis in patients at high risk of developing breast cancer as well as in those who experience bleeding or spotting during standard therapy [45, 46]. Phytoestrogens are plant components with estrogenic activity and potential positive therapeutic intervention in menopausal symptoms. The most well-known source of origin is vegetables, especially soy. According to epidemiological studies, they have a favorable effect on the remission of

vasomotor symptoms. On the contrary, they are less effective in terms of their action in the atrophy of the genitourinary system. It has been reported that in women with mild and moderate symptoms and a contraindication to the application of HRT, the enrichment of the diet with foods rich in phytoestrogens may be beneficial. Finally, in the long term, soy may protect the cardiovascular system while, on the contrary, its effect on osteoporosis needs further investigation [47].

#### **4. Ways of administration**

The modes of administration for the specific formulations of hormone replacement therapy (HRT) are primarily twofold: oral and parenteral, with the latter further categorized into injectable transdermal and local methods.

Oral steroids are more common. Oral steroids, after being absorbed from the gastrointestinal tract, pass through the liver before entering the general circulation. This results in a small fraction (5%) of active substances entering the general circulation. Oral estrogens stimulate the production in the liver of substances with possible adverse effects such as coagulation factors and angiotensinogen, but they rapidly increase HDL and decrease LDL as a consequence of the first-pass effect [48]. The advantages include the possibility of daily interruption of treatment or reducing the dose in case of adverse effects or, conversely, the possibility of increasing the dose. It also allows the application of monotherapy or combined therapy through a wide variety of independent formulations. Parenteral therapy is available either for daily use or for longer periods of time (up to 6 months). Daily administration is used for rapid resolution of vasomotor symptoms after surgical removal of the ovaries. As with oral, it is possible to stop or reduce the dosage on a daily basis. Monthly or longer dosing has the disadvantage of losing the ability to stop immediately but offers the advantage of constant checks by the attending physician. Parenteral administration bypasses the first pass through the liver and does not stimulate hepatic metabolism [49]. Of the other types of parenteral administration, the subcutaneous implant maintains stable estrogen levels for approximately 6 months. It is more useful for women with good estrogen tolerance because it is not possible to stop treatment quickly. The transdermal patch is placed on the skin and gradually releases estrogen or estrogen and progesterone into the circulation. It is replaced every 3–7 days. During its stay on the skin, it releases steroid hormones at normal levels [50]. The local route is indicated for the treatment of atrophic disorders such as vaginitis and vulvitis. It mainly contains the biologically weaker estrogen, estriol. It is administered mainly in the form of a ring or suppository cream [51]. With regard to the types of HRT, the treatment is divided into monotherapy which includes a steroid, and combined treatment which mainly includes two types of steroid hormones. Estrogen monotherapy is only indicated in patients who have undergone hysterectomy. Cyclic combination therapy, involving a treatment-free interval, closely mimics the hormonal profile of reproductive age. This approach is particularly popular in the pre- and peri-menopausal periods. The periodic addition of progestogen often results in breakthrough bleeding, occurring either during the progesterone phase or following both types of treatment, an effect not resisted by premenopausal women with regular menses. Moreover, women experiencing irregular cycles find benefit in the normalization of these cycles through progesterone. Conversely, some women initiating hormone replacement therapy (HRT) a few years after menopause may perceive the return of menstruation as a drawback, leading them to discontinue the treatment. Continuous combination therapy is utilized to enhance tolerance, reduce bleeding, or achieve complete amenorrhea, particularly in postmenopausal

women. The uninterrupted administration of tibolone is also considered a viable solution for women who have been in a menopausal state for at least 1 year. Additionally, some propose the inclusion of progestogen for extended durations (3–6 months) with the aim of prolonging the period of menstruation-free intervals; however, it should be noted that there is no conclusive evidence documenting that this method provides protection to the endometrium [49–51].

## **5. Modus and duration of administration**

Typically, the initial prescription spans 3 months, with a subsequent course extending to 6 months of administration. Remission of vasomotor symptoms is observed after a few weeks of satisfactory treatment. The pace of improvement in urogenital symptoms is gradual, as it necessitates approximately 6 months for the estrogenization of the vagina to take effect. Finally, a reassessment of the effectiveness of the therapeutic treatment is required on an annual basis [49]. There is no agreement regarding the duration of the therapeutic treatment. Some argue that it should be applied until symptoms subside. Usually, a treatment of 3–5 years is sufficient for the complete remission of the symptoms without excluding the relapse upon interruption, in which case a repetition of the treatment is necessary. Relapse is inevitable with regard to the symptoms of urogenital atrophy. Discontinuation of treatment without medical consent is often due to events that occur during this period at the woman's age, such as retirement or the occurrence of breast cancer in a relative or friend. However, in any case, for the continuation of the treatment for a long period of time, the possible slightly increased risk of breast cancer and thromboembolic events should be taken into account. The modern opinion regarding hormone replacement therapy is that it should be given to perimenopausal and early menopausal women without contraindications and after systematic information about the possible risks and benefits. It is not recommended to start the treatment after the age of 60. In women with early menopause <40 years or early menopause <45 years, it is recommended to administer replacement with sex hormones until the age of 51 for the treatment of vasomotor symptoms, and for the prevention of osteoporosis and cardiovascular diseases [49].

## **6. Surgical menopause**

The frequency of oophorectomy varies depending on the age of the woman and the indication for which the operation is performed. Oophorectomy is performed in 75% of women with cancer or precancerous conditions [50], and in 52% with benign diseases during abdominal surgery, while only in 20% when access is vaginal. There is no unanimity on the necessity of oophorectomy and on its indications in benign diseases. In many cases, the decision is arbitrary and based on some age limit. An important role in these decisions must be played by the woman's desire for balanced information about the benefits and harms of ovarian conservation. Although this seems commonplace, in reality, women are affected by counseling, which is usually lacking. It is typical in one paper that 20% of women who have undergone oophorectomy during hysterectomy did not know that the ovaries have been removed [51]. In general, hysterectomy with oophorectomy is more commonly performed in women with a lower educational level, obesity, and nulliparous women [52].

## **6.1 Hormone replacement therapy after hysterectomy**

Before deciding to remove functioning ovaries, there should be ways to replenish their function for long periods of time without health consequences. It is a fact that young women, even after the preservation of the ovaries in hysterectomy, often experience hot flashes and other symptoms of estrogen deficiency that are not related to the hormonal picture [53], while others (up to 50%) tolerate the ovarian failure caused by salpingo-oophorectomy relatively well. Sometimes, while preserving the ovaries, replacement therapy is not given and their insufficiency is not recognized, resulting in unwanted cardiovascular effects [54–56]. The existing preparations with conjugated estrogens, estradiol, and various types of progesterone are far from the normal secretion of the ovary, although they substitute to a large extent at the cost of some risks. These include thromboembolic disease, cholecystopathies, and to a lesser extent the risk of breast cancer. Hypertension may occur during the administration of hormone replacement and it may be necessary to stop it. The most serious practical problem is non-compliance with chronic treatment. Speroff et al. [57], in a review of the literature, observed that adherence to treatment ranged from 31% to 89% at baseline and, after 5 years, varied between 13% and 71%. If a woman who undergoes oophorectomy at age 35 does not adhere to the treatment, it is estimated that she may experience a reduction in life expectancy by 1.4 years. However, the absence of hysterectomy bleeding and the variety of formulations help with compliance. Woodman and Read [58] reported compliance up to 84.3% at 4 years, but in 64.5% they had to change the initial formulation. The surgeon should resist the temptation to remove the ovaries in a menstruating woman. Such a decision, as technically easy as it may seem, has significant implications for her overall health. Arbitrary age limits cannot justify such an act unless the woman is at or approaching menopause. The patient's opinion will be mainly taken into account after being informed about the benefits and risks of ovarian reserve in combination with her history. Factors to be considered are infertility, infertility, hereditary risk of cancer, risk factors for cardiovascular disease or osteoporosis, carcinophobia, views on hormone replacement, and its psychological background. After all, the art of medicine is to adapt the patient's needs and desires to what is best for maintaining his health. HRT is effective in preventing bone loss associated with menopause. HRT reduces the incidence of all (osteoporosis-related) fractures, including spine and hip fractures, even in low-risk patients. Even with lower doses of estrogen, most women have improvements in bone mineral density, even though the reduction in bone loss is dose-dependent [50, 51, 56]. When it comes to women who are younger than 60 years old and have entered early menopause, hormone replacement therapy (HRT) is the recommended initial course of treatment for preventing osteoporosis. After treatment is stopped, HRT's protective effect on bone mineral density decreases, albeit in certain situations some protection endures. It is not advised to begin HRT treatment after the age of 60 in order to prevent fractures alone. Age has a major impact on how safe HRT is. Recent data and a re-evaluation of older studies indicate that, for the majority of women, hormone replacement therapy (HRT), when initiated within a few years of menopause and with clear indications, tends to offer more benefits than risks. An important observation that should be explained to women, is that HRT reduces mortality (by about 30%) when administered to women <60 years of age, perhaps because of protection against coronary heart disease. The decision to initiate a woman's HRT must be individualized. The actual opinion regarding hormone replacement therapy Timbolone, a phytoestrogen, is that it should be administered to perimenopausal and early menopausal women without contraindications and after systematic information about potential risks and

benefits. It is not recommended to start treatment after the age of 60. In women with premature menopause <40 years old, it is recommended to administer replacement with sex hormones until the age of 51 years for the treatment of vasomotor symptoms, and for the prevention of osteoporosis and cardiovascular diseases [56]. The increase in life expectancy up to 82 years, results in a woman living about 30 years with problems appearing during menopause. The significant decrease in ovarian estrogens is responsible for the appearance of changes in many organ systems and in general in the life of the menopausal woman. This reduction, in addition to the annoying symptoms that afflict the woman when she enters the climacteric period, is also responsible for “asymptomatic”—insidious effects that affect many organ systems, such as the vagina, uterus, urethra, urethra bladder, breast, skin, heart and blood vessels. It is understood that, with such an effect on this multitude of organ systems, the possibility of dangerous conditions for the health and quality of life of the menopausal woman is increased. In Western societies, the quality of life in menopause is considered an inalienable right and necessity, as a result, in recent decades, research has been carried out that examines the range and severity of the symptoms that accompany it. The necessity—and subsequently the appropriateness—of the various therapeutic methods that have been developed has become a dominant issue of disagreement. Health professionals must be informed about the developments in the field of menopause and contribute to the improvement of the quality of life of menopausal women.

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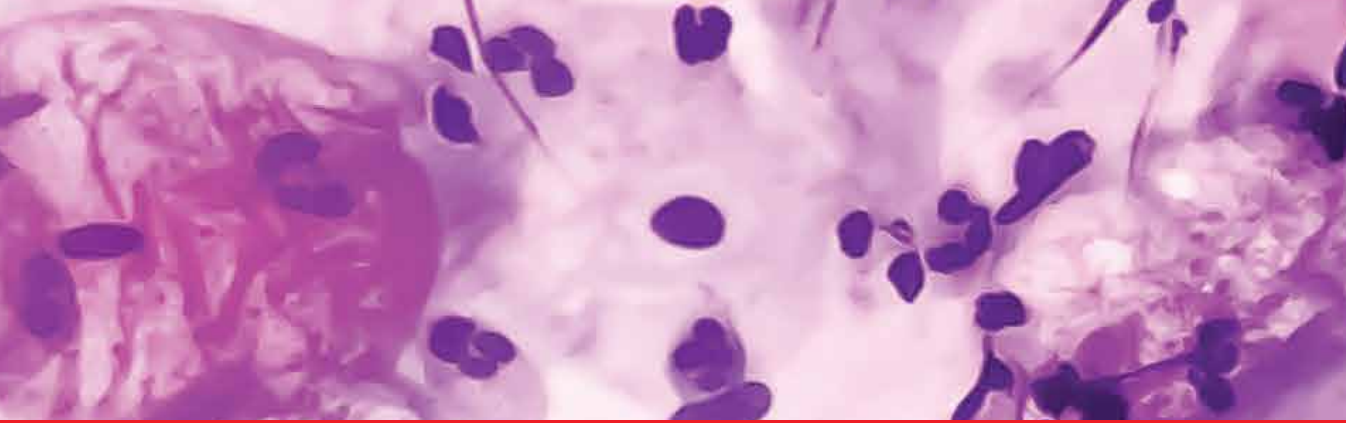
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*Reproductive and Gynecologic Health Annual Volume 2025* reviews conditions and pathology affecting the female reproductive system across the lifespan. It provides an overview of fetal growth, cervical and endometrial cancer, and postmenopausal care of women in detail. This book is intended as a valuable resource for patients, clinicians, researchers, and ancillary healthcare staff, as it explores comprehensive care for women through all stages of reproductive life. It should serve as a guide to providing the best care for women throughout their lives.

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