

# Pathologically Increased Endometrial Thickness in Ultrasound Examination: Causes, Diagnosis and Treatment

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## Abstract

Thickened endometrium is a routine finding that can be seen in an ultrasound examination of a woman. Proliferation of the endometrium can be induced either due to non-pathological causes (i.e. during menstrual cycle and pregnancy), to pathological causes (i.e. in endometrial

hyperplasia, cancer, presence of a polyp, polycystic ovarian syndrome (PCOS) or to certain drugs (i.e. tamoxifen and HRT - hormone replacement therapy).

**Keywords:** Endometrial hyperplasia, endometrial thickness, endometrial cancer

## Introduction

The endometrium is, anatomically, the inner lining of the uterus and under hormonal influence is responsible for the menstrual cycle of the females. TVS (transvaginal scan) examination of the endometrium requires a meticulous and systematic technique. The right way of measuring the endometrium is to perform a TVS on day 4, 5 or 6 of the menstrual cycle when the endometrium is expected to be its thinnest. The examiner should scan the uterus in a sagittal view and measure the anteroposterior endometrial thickness (from one basal layer to the other), excluding the presence of any fluid within the cavity. In reproductive

age patients the endometrial thickness varies from 2-9 mm in the proliferative phase to 15-20 mm in the secretory phase of the cycle. In postmenopausal women an endometrial thickness below 4 to 5 mm is associated with a low risk of endometrial disease. Additionally, normal proliferation of the endometrium is seen in very early pregnancy as a response to hormonal changes.

Apart from these physiological changes of the endometrial thickness, there are several pathological causes that can lead to abnormal changes of the endometrium during the reproductive and the postmenopausal period in a female life<sup>[1,2]</sup>.

## Pathological causes of increased endometrial thickness

### 1. Endometrial hyperplasia

**Definition:** abnormal proliferation of the endometrium. In most cases, endometrial hyperplasia results from high levels of estrogens combined with insufficient levels of progesterone which counteracts estrogens proliferative effects. It can be seen in both reproductive and postmenopausal age<sup>[3,4]</sup>.

**Risk factors:** Obesity, hypertension, polycystic ovarian syndrome, nulliparity, diabetes, HRT (hormone replacement therapy) and tamoxifen intake.

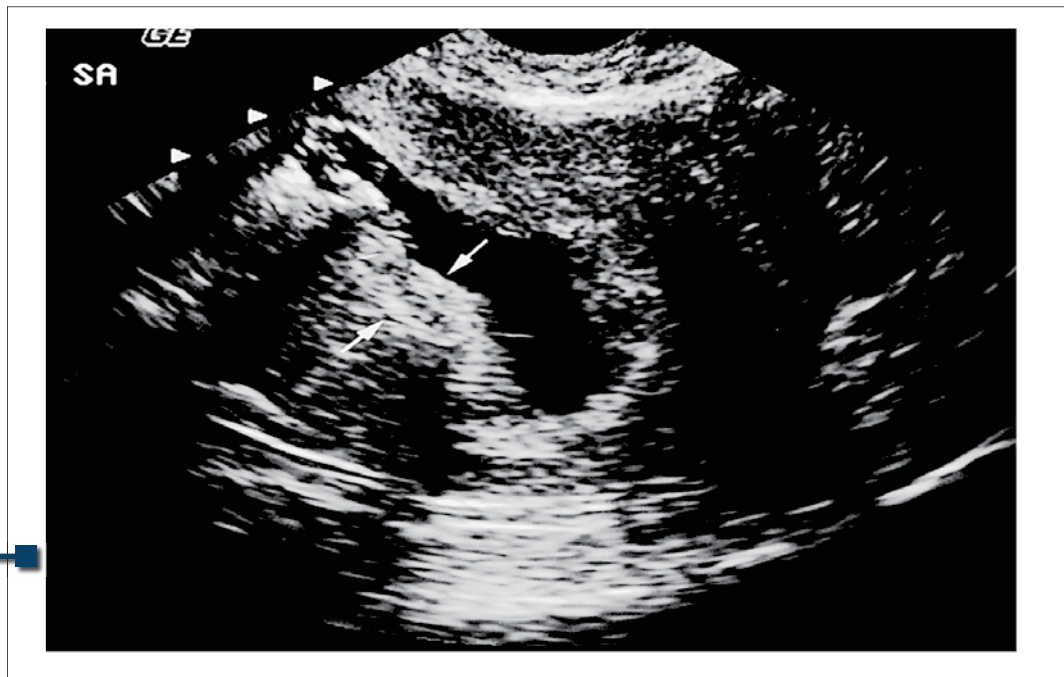


Figure 1. Irregular endometrium in endometrial hyperplasia during hysterosonography

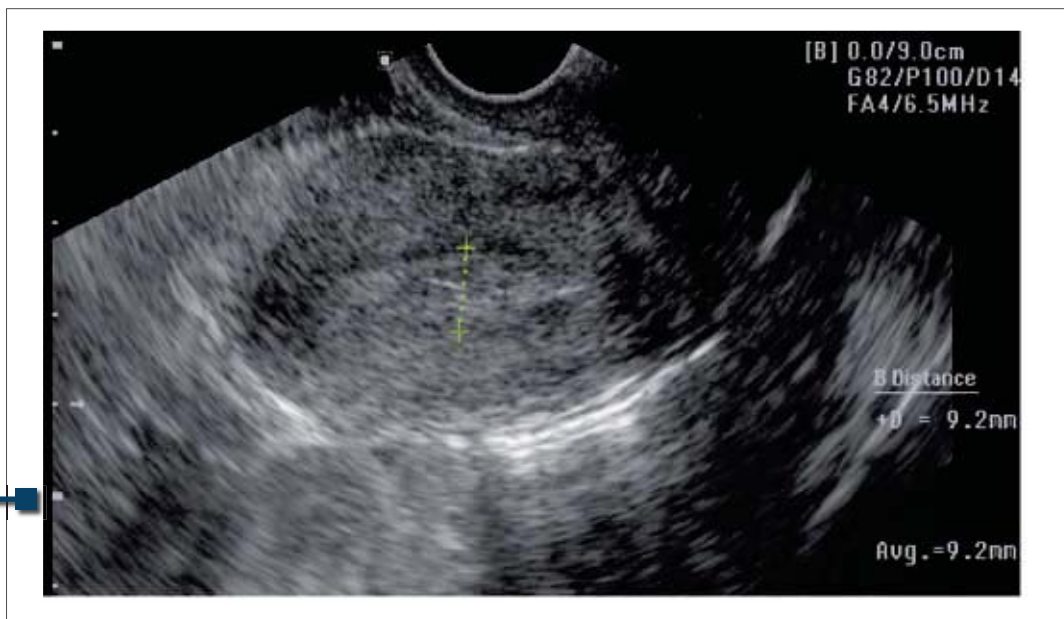


Figure 2. Vaginal ultrasound. Endometrial hyperplasia in postmenopausal woman

#### Symptoms and findings:

- Abnormal uterine bleeding (menorrhagia, intermenstrual bleeding or spotting, postmenopausal bleeding) is the first symptom in women with endometrial hyperplasia.
- Presence of atypical glandular cells found in a Papanicolaou smear.
- Thick, cystic and irregular endometrium aspect in ultrasound scans<sup>[3,4]</sup> (figures 1, 2).

#### Histological types:

- Hyperplasia without atypia (simple or complex). In simple hyperplasia (called also “cystic hyperplasia” in the past) the glands histologically have a “Swiss cheese” appearance. Untreated, 1% of simple hyperplasia will progress to endometrial cancer in a period of 15 years while in complex hyperplasia without atypia 3% will progress to cancer.

In general, the hyperplasia without atypia have very good prognosis and respond very well to progestin therapy and it is not consider as a premalignant lesion<sup>[3]</sup>.

- Hyperplasia with atypia (simple or complex). Histologically, it is characterized by endometrial glands with increased nuclear: cytoplasmic ratio. The nuclei are irregular and the glands have increased mitotic

activity. This type of hyperplasia can be characterized as a precancerous state (endometrial intraepithelial lesion) since 8-29% will progress to endometrial cancer. About 80% of lesions can regress with progestin therapy but the relapsing rate after stopping therapy is high. In patients with hyperplasia with atypia, approximately 25% will have endometrial carcinoma in the final histology<sup>[4]</sup> (figures 3, 4, 5).

#### Diagnosis

A thorough medical history focused to the history of the menstrual cycle and a transvaginal ultrasound, which must be better performed on the proliferative phase of the cycle, can lead to the first step of diagnosing endometrial hyperplasia. For a definitive diagnosis, an endometrial biopsy must be performed either by an office pipelle biopsy or by MedGyn EndoSampler (FDA approved-[www.medgyn.com](http://www.medgyn.com)) or by a D&C alone or by hysteroscopy and biopsy<sup>[3,4]</sup>. Interestingly, a study performed by Ancăr *et al* showed that the combined methods of transvaginal scan and cytology of endometrial sample taken with the Cornier's pipelle seems to be the method of first choice in diagnosing simple endometrial hyperplasia while the classical biopsy is most valuable in diagnosing complex hyperplasia<sup>[5]</sup>.

#### Treatment

##### 1. Endometrial hyperplasia without atypia

Start progestin therapy (Medroxyprogesterone acetate, Dihydrogesterone, Norethisterone 10-20mg twice daily) continuous or cyclically for 3 months.



Repeat TVS or D&C(dilation & curettage) if needed and check if symptoms persist.



If hyperplasia is treated, then we can continue with low dose progestin for 10 days per month for 12 months. Annual TVS endometrium screening is advisable.



If hyperplasia persists then



Try a higher dose of progestin (e.g Medroxyprogesterone acetate 40mg/day for 3 months)



Persistent hyperplasia → Proceed to total hysterectomy<sup>[3]</sup>.

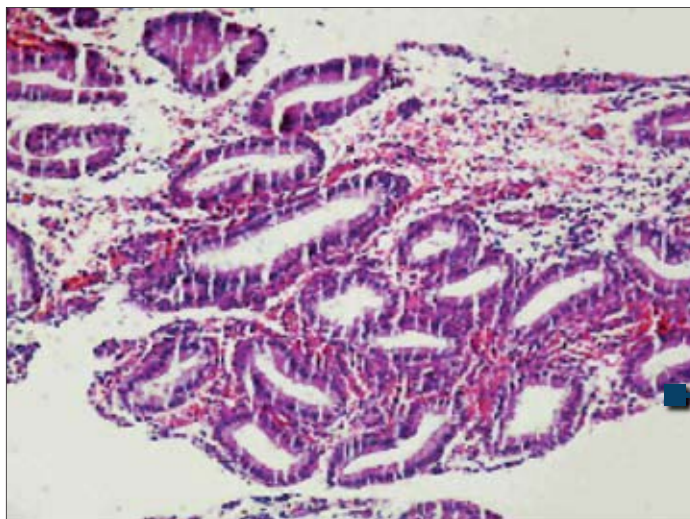


Figure 3. Simple endometrial hyperplasia without atypia

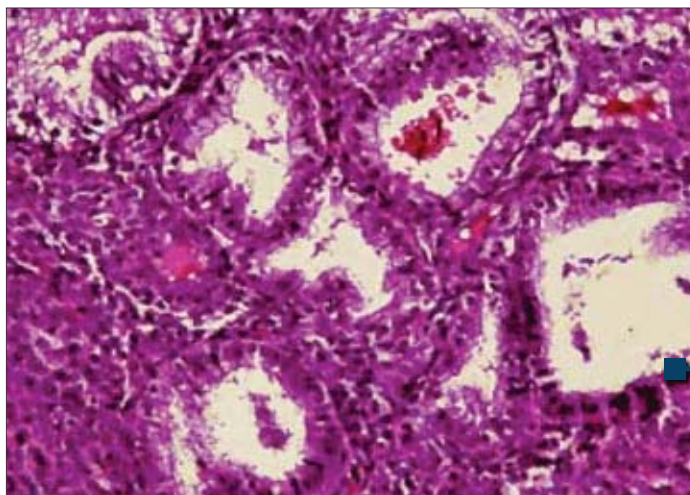


Figure 4. Complex endometrial hyperplasia without atypia

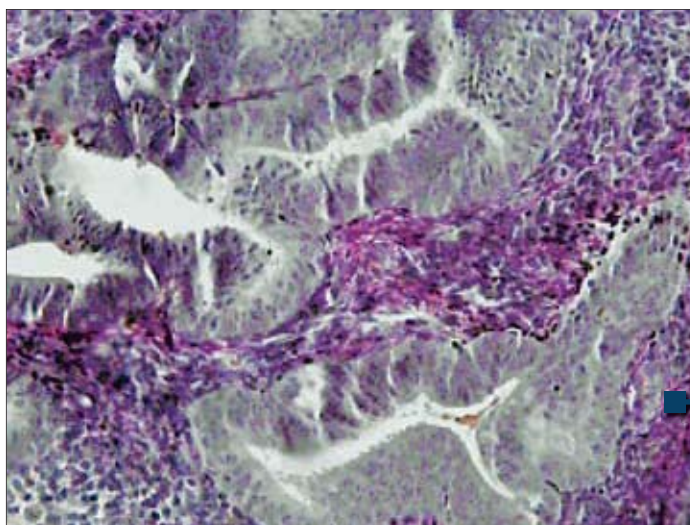


Figure 5. Complex endometrial hyperplasia with atypia

Endometrial hyperplasia without atypia can also be treated by the insertion of a progesterone coated coil but it is more difficult to access the treatment and the endometrium by scan.

Another aspect for the prevention and treatment of endometrial hyperplasia and cancer was recently reported by Linkov *et al* in a large review of disease risks. They concluded that existing therapies for endometrial hyperplasia target hormone imbalance, which is just one aspect of endometrial cancer development. Next generation therapies for endometrial hyperplasia and cancer should also include diet, exercise, weight loss, control of hypertension and diabetes<sup>[6]</sup>.

## 2. Endometrial hyperplasia with atypia.

Definite treatment is hysterectomy since this lesion can be characterized as precancerous. There is a long discussion in the management of nulliparous women. Some may treat the patient with very high doses of progesterone (megestrol) and then advise the woman to get pregnant soon and then proceed to hysterectomy. All the management should be discussed with the patient and the risks of it should be considered.

Recently, Shen *et al* found that metformin and oral contraceptive pill can be used for the treatment of atypical endometrial hyperplasia complicating polycystic ovarian syndrome where high doses of progestin therapy failed to revert the hyperplasia. This suggests that insulin resistance might play a role in the occurrence of atypical hyperplasia in the presence of PCOS<sup>[7]</sup>.

## 2. Endometrial Polyps

**Definition:** It's a structure in the lining of the uterus that occupies either a small or large space within the cavity. A polyp may have a spheroid or cylindrical shape, with a stalk base (pedunculated polyp), or a flat broad base (sessile polyp).

**Pathology:** Endometrial polyps can be seen in reproductive and postmenopausal age and answered in more than 25% of the females. These are protuberant lesions on the surface of the endometrium containing an irregular distribution of endometrial glands with thick walled blood vessels and range from few millimeters to big masses that cover the entire uterine cavity. Polyps are usually benign but the risk to transformed in to endometrial carcinoma is 0.8-4.8%<sup>[8]</sup> (mean 2%). One large study by Antunes *et al* found that a prevalence of 3.8% of premalignancy or malignancy was observed in polyps resected by hysteroscopy (1% hyperplasia with atypia and 2.7% endometrial carcinoma)<sup>[9]</sup>. The frequency of malignant endometrial polyps increases when ageing, especially for patients aged 65 or more. Additionally postmenopausal bleeding is a risk factor associated with premalignancy or malignancy of endometrial polyps.

**Etiology-Risk factors:** There is no known, definite cause for the development of endometrial polyps but they seem to be affected by hormone levels and to grow in response to circulating estrogens. In one theory endometrial polyp begins when a stromal cell undergoes a rearrangement in chromosome 6p21 resulting in an abnormal signal to grow. Also for develop-

ment of an endometrial polyp the mechanism for the regulation of apoptosis expressed by Bcl-2 would appear to have been lost, resulting in an increase in cell longevity.

Obesity, high blood pressure, unopposed estrogens intake are the main risk factors for the development of endometrial polyps. Additionally a personal history of tamoxifen intake increases the risk by 12-25%. Tamoxifen related polyps are different. They are larger (5 cm) and differentiated microscopically by a combination of proliferating activity, aberrant epithelial differentiation and focal periglandular stromal condensation<sup>[10]</sup>.

### Symptoms & Signs:

Endometrial polyps are sometimes asymptomatic and can be found accidentally in routine ultrasound scans, but they can usually cause several symptoms (i.e. intermenstrual bleeding, spotting, menorrhagia, and dysmenorrhea). Additionally the presence of an endometrial polyp can be a cause of infertility or of recurrent miscarriages in otherwise asymptomatic patients. In those cases an endometrial polyp can lead to failed implantation of an embryo. Finally in elder women they can be responsible for postmenopausal spotting or bleeding

### Diagnosis

A good knowledge of the medical history, a transvaginal ultrasound with the help of sonohysterography can lead to the diagnosis of an endometrial polyp. A definitive diagnosis is done by diagnostic hysteroscopy (direct visualization of the lesion - figures 6, 7).



Figure 6. Endometrial polyp in sonohysterography



Figure 7. Hysteroscopic view of a polyp

### Treatment

Generally, endometrial polyps should be removed in all elderly women and whenever postmenopausal bleeding is present. In younger asymptomatic women with no risk factors and no fertility issues it may be possible to avoid routine removal in order to minimize surgical risks, performing a close follow-up.

Endometrial polyps can be removed using either the "blind" technique D&C or by direct vision during hysteroscopy (using scissors or the loop diathermy).

In D&C sometimes the lesion may be missed or incompletely removed and the symptoms of the patient may persist after the operation. The preferred method is the hysteroscopic resection of the polyp because it is less traumatic, especially in younger women, and more precise. Hysteroscopy today considered the gold standard method for the diagnosis and treatment of endometrial polyps with very high specificity and sensitivity rates.

However, whatever method we choose, it is really important to remove the whole polyp including its base (the point of insertion of the stalk into the endometrium - myometrium) because there is a risk (1%) for adenocarcinoma to arise from the base and not from the body of the polyp<sup>[11]</sup>.

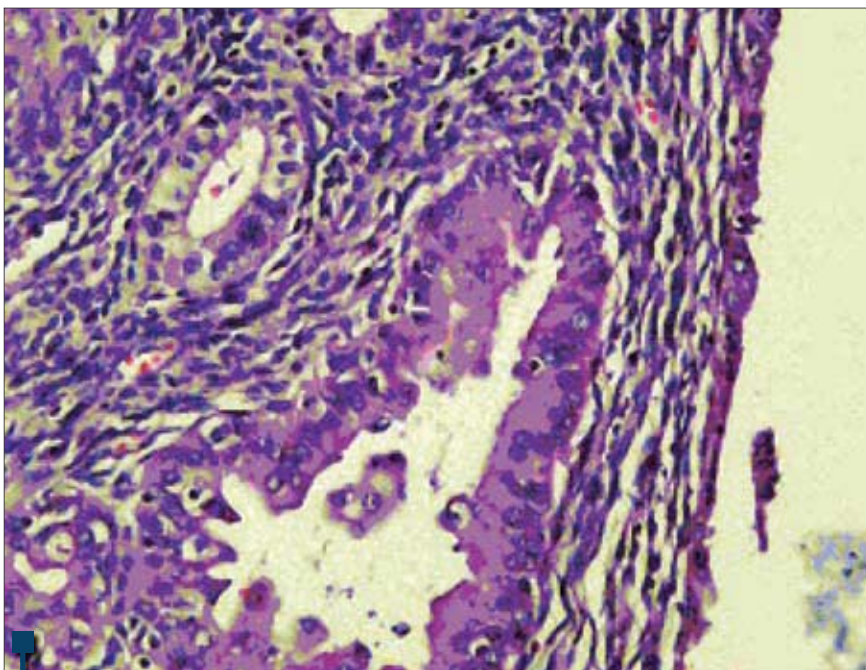


Figure 8. Endometrial Adenocarcinoma

### 3. Endometrial cancer

#### Introduction

Endometrial cancer originates in the endometrium. The peak incidence is between the sixth and seventh decade, but it can also occur in women in their forties (less frequently: 2-5%) or aged less than 20-30 years (rarely). Endometrial carcinoma is the most common pelvic genital cancer in women

#### Risk factors

Estrogens have been implicated as a causal agent in the development of endometrial carcinoma. Alterations of their metabolism and those who take unopposed exogenous estrogens may cause the disease. This exposure results in elevated mitotic proliferation of endometrial cells which in turn increases the risk of DNA replication errors and DNA mutations which can lead to endometrial cancer.

Associated conditions which may induce endometrial cancer are:

- Obesity (increased estrogen due to aromatization of estrogens to the adipose tissue, 10 fold).
- Hypertension (1.5 times).
- Diabetes mellitus (2.8 times).
- Polycystic ovarian syndrome (long anovulatory cycles- unopposed high estrogen levels). Additionally in PCOS the interaction between estrogen, insulin and IGF1 - insulin growth

factor - maybe more important than hyperestrogenemia alone.

- Nulliparity (2 times).
- Infertility.
- Early menarche, late menopause (2.4 times).
- Endometrial hyperplasia, especially with atypia.
- The use of Tamoxifen and Toremifen for 5 years induces a relative risk of around 6.0 for the development of endometrial cancer.
- Personal history of ovarian, colon, breast cancer. Family history of endometrial cancer. Finally, women with hereditary non polyposis syndrome carry a lifetime risk up to 30% of developing endometrial cancer.
- Low socio-economic status.
- Antipsychotic drugs, mainly due to their side effects (obesity, insulin resistance, amenorrhea)<sup>[3,4,8,12]</sup>.

Interestingly smoking is associated with a reduced risk of endometrial cancer due to antiestrogenic effect of nicotine<sup>[13]</sup>. High parity also have a protective effect against endometrial cancer possibly due to high progesterone levels during pregnancy and the mechanical removal of the premalignant cells with each delivery. Additionally, in a large cohort study, Patel *et al* found that women undergone light and moderate physical activity had a lower risk to suffer from endometrial cancer, especially among women who were overweight or obese<sup>[14]</sup>.

Finally one study by Iatrakis *et al* showed that the BMI (body mass index), parity, type of menstrual cycles, history of polycystic ovarian syndrome and diabetes are possibly related to endometrial cancer in women younger than 50 years old and the strongest relation was found with increased BMI<sup>[15]</sup>.

#### Classification of endometrial carcinoma<sup>[3, 4]</sup>

**1. Endometrioid Adenocarcinoma:** this is the commonest type of endometrial cancer corresponding approximately to 70-80% of all the cases (figure 8).

**2. Adenocarcinoma with squamous differentiation:** it makes up approximately to 5% of all endometrial carcinomas.

**3. Adenosquamous carcinoma:** represent the 10-20% of all the cases.

**4. Pappillary Serous Carcinoma:** histopathologically this type of cancer resembles the ovarian cancer and

patients should be treated in a similar manner as those with ovarian cancer. This type, affect the older women and is not associated with hyperestrogenic state and represent the 5-10% of all cases.

**5. Clear cell carcinoma:** This is an aggressive type of endometrial cancer, it occurs in elderly women and like the serous type is not associated with a hyperestrogenic state and can be found in about 5% of the cases.

#### 6. Miscellaneous subtypes:

Mucinous  
Secretory  
Squamous cell } carcinomas

#### Grading of endometrial carcinoma

Grade 1 (G1) less than 5% of the tumor shows a solid growth pattern

Grade 2 (G2) 6-50% of the tumor shows a solid growth pattern

Grade 3 (G3) more than 50% of the tumor shows a solid growth pattern

#### Symptoms - signs of endometrial cancer

5% of affected women are asymptomatic. In those cases endometrial cancer can be detected as a result of investigation of an abnormal Pap smear (e.g presence of endometrial or atypical glandular cells) or in a random investigation for an unrelated reason (TVS or CT of the abdomen).

Women in premenopausal age may complain for:

- Abnormal bleeding occurs in 80-90%. This bleeding can be described either as spotting, metrorrhagia, menorrhagia or a combination of both. Intermenstrual bleeding can also be a related symptom.

- Abdominal pain and discomfort can be the main complain (at presentation) in more advanced stages of the disease.

In elder women, postmenopausal bleeding or spotting is the major complain in case of endometrial cancer. Additionally an increased vaginal discharge can be the first symptom. The discharge can be simple or purulent with abdominal pain due to pyometra. This can occur because of cervical stenosis and accumulation of blood into the endometrial cavity.

#### Diagnosis and differential diagnosis of endometrial cancer

Abnormal bleeding due to endometrial atrophy, endometrial polyp, endometrial hyperplasia, use of HRT, presence of a submucous fibroid can cause similar symptoms as endometrial cancer and should be evaluated.

Table 1

#### Figo staging and 5 year overall survival of endometrial cancer

Stage		5 year survival
Ia	Tumor limited to endometrium	90-95%
Ib	Tumor invades < 50% of the myometrium	90%
Ic	Tumor invades > 50% of the myometrium	80.7%
IIa	Endocervical glandular involvement only	79.9%
IIb	Cervical stromal invasion	72.3%
IIIa	Tumor invades uterine serosa and or adnexa and/or positive peritoneal cytology	63.4%
IIIb	Vaginal metastases	38.8%
IIIc	Metastases to pelvic and/or para-aortic lymph nodes	<30%
IVa	Tumor invasion of the bladder or bowel	<10%
IVb	Distant metastasis including intra-abdominal or inguinal lymph nodes	5%

The first diagnostic step of endometrial cancer is an abdominal or, even better, a transvaginal ultrasound. Thick endometrium after menstruation (in reproductive age women) and an endometrial thickness exceeding 4-5 mm in postmenopausal women needs further investigation. In postmenopausal woman with vaginal bleeding the risk of cancer is approximately 7.3% if the endometrium exceeds 5 mm while endometrial thickness below 5 mm coincides with endometrial cancer in only 0.07%<sup>[16]</sup>. The Papanicolaou smear is an inaccurate diagnostic tool because only 30-40% of patients with endometrial cancer will have an abnormal Pap smear. A definitive diagnosis of the disease is achieved by the performance of a D&C or hysteroscopy and biopsy.

Apart from the traditional hysteroscopy or D&C which are used by most specialists, recently a new method has been introduced called the TruTest. This test can be done in office gynecology setting without the need of anesthesia. The TruTest uses the so called Tao Brush to brush the entire lining of the uterus. It is less invasive and less painful, and can be performed at the same time with a routine Pap smear thus allowing very early detection of endometrial cancer especially in high risk population<sup>[3,4]</sup>.

#### Pretreatment evaluation of endometrial cancer

1. Physical examination should be performed with attention on palpation of abdominal masses, lymph nodes and possible areas of cancer spread within pelvis. Cervix, vagina, parametria and adnexae should be examined thoroughly for metastases.

2. Determination of serum markers (Ca 125, CEA, AFP, Ca 19-9, Ca 15-3, SCC) may help to evaluate the severity of the case. Serum Ca 125 is elevated in 80% of patients with advanced epithelial ovarian cancer but it is also elevated in most patients with advanced or metastatic endometrial cancer. At cut off level of 40 U/ml Ca 125 indicate nodal metastases with sensitivity of 77.8 % and specificity of 81.1 %<sup>[12]</sup>.

3. Chest x-ray or even a CT should be performed preoperative in order to exclude pulmonary metastases.

4. MRI of the pelvis, positron emission tomography (PET) and 3D sonography may help us to deliver more information about the invasion depth of the myometrium. By this way the surgeon can plan the operation better in respect to proceed or not to pelvic side wall lymph node sampling<sup>[17]</sup>. Additionally, CT scan can depict distant metastases (liver, bowel).

5. Rectoscopy, cystoscopy, IVP (intravenous pyelography), bone scan are procedures that can be reserved in patients with more advanced disease.

Table 2

**Indications for pelvic and paraaortic lymph node dissection**

- Myometrial invasion > 50%
- Tumor size > 2 cm
- Cervical involvement
- Distant metastases

**Treatment of endometrial cancer  
Surgery**

Surgery is the treatment of choice in all stages of endometrial carcinomas. Abdominal hysterectomy (with longitudinal incision for a better exposure) with removal of the adnexae and peritoneal washings is the standard procedure. A delayed exploration of the whole abdomen and pelvis has to take place, investigating especially the diaphragm, the liver and the omentum. After the removal of uterus the depth of invasion into the myometrium should be determined. If the invasion exceeds 50% then pelvic and para-aortic lymphadenectomy should be performed. For appropriate staging more than 10 lymph nodes need to be excised (table 2).

Apart from the traditional open laparotomy endometrial cancer can nowadays be operated laparoscopically, in special centers, with great success rates since throughout the past 15 years the technique has greatly progressed. Seracchioli et al have recently made a review about laparoscopic treatment of endometrial cancer<sup>[18]</sup>. They found that surgical staging for endometrial cancer, by laparoscopic hysterectomy, is feasible and well tolerated from the patients and by this way they reduce the perioperative morbidity and postoperative pain. This surgical approach does not seem to affect recurrence of the disease and the overall survival rates. Another study by de la Ordsen et al showed that short term results (hysterectomy technique, lymphadenectomy extent, postoperative pain, intra- and postoperative complications, patient recovery and quality of life) of laparoscopic hysterectomy as elective therapy for endometrial cancer are at least equivalent if not even better than open surgery results; long term results seems equivalent but more studies are needed in this area. Overall laparoscopic hysterectomy should be performed by

experienced surgeons and need to be evaluated in the future due to its limitations<sup>[19]</sup>.

**Postoperative adjuvant therapy**

Patients generally can be classified into three main treatment categories

1. Low risk with stage Ia G1, G2 (no myometrial invasion): no need for postoperative treatment.

2. Intermediate risk from Ib to IIIa stage (myometrial invasion and positive cytology): need vaginal cuff and/or pelvic irradiation depending from the stage of the disease.

3. High risk from IIIa G1, G2, G3 to IV (adnexa involvement, distant metastases): pelvic and vaginal irradiation and/or whole abdomen irradiation and/or systemic chemotherapy depending on the exact stage of the disease.

**Postoperative Follow up**

Patients treated for endometrial cancer should be examined every 4 months for the first 3 years, every 6 months thereafter up to 5 years, and then on a yearly basis. Physical examination is the gold standard with emphasis on the examination of the abdomen, pelvis, vagina and peripheral lymph nodes. Vaginal Pap smear and transvaginal ultrasonography can be helpful for early diagnosis of recurrences. Additionally a CT scan of the upper and lower abdomen can be performed annually for the first 3 years. Chest x-ray every 6 months is also an important method for the postoperative patient follow-up. Finally, measurement of Ca 125 can be used for the follow up. Up to 95% of all the recurrences can be detected by this way. Most of the recurrences of the disease have been reported the first 3 years of the primary treatment. Vaginal bleeding, abdominal pain and even hemoptysis (in lung metastases) are common symptoms which need further evaluation. Recurrences can be treated by radiotherapy alone or in combination with surgery, by the

use of tamoxifen or by the use of high doses of medroxyprogesterone acetate. Treatment should be individualized according to the site, size of the recurrence and the physical state of the patient.

Endometrial cancer is a disease that affects the elder women; there is no specific screening test but it has a very good prognosis if detected early<sup>[12]</sup>.

**Preservation of fertility**

Preservation of fertility in young women who develop endometrial cancer is an option but still in an experimental stage and patients should be informed. Hormonal therapy with megestrol acetate at 160 mg/day for 3 months or medroxyprogesterone acetate (MPA) at 200-800 mg/day for 2-14 months resulted in disease regression in 60 to 75%, however, the percentage of patients who actually delivered healthy children was 20-25%. Only selected patients can follow this protocol. Patients with well differentiated type of endometrial cancer, minimal endometrium invasion and with favorable prognosis can be candidates. In these cases it is important to monitor the response of the therapy and exclude recurrence by performing serial endometrial biopsies every three months.

**HRT and endometrial cancer**

The use of hormone replacement therapy, in order to alleviate menopausal symptoms with or without progesterone hasn't increased the endometrial cancer recurrence risk. Further more the introduction of new generation of SERM-selective estrogen receptor modulator (raloxifene, idoxifene) can offer new means of treatment in those cases without influencing the endometrium.

**4. Polycystic ovarian syndrome**

PCOS is a common disorder affecting about 10% of the women. It has been first described in 1935 by Stein and Leventhal.

According to the Rotterdam criteria (May 2003) PCOS is defined by the presence of two of the following three features: 1) oligomenorrhea or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, 3) polycystic ovaries seen in ultrasound<sup>[20]</sup>. Polycystic ovary is defined as an ovary with 12 or more follicles measuring 2-9 mm in diameter and/or increased ovarian volume (>10 cm<sup>3</sup>)<sup>[21]</sup>.

Polycystic ovarian syndrome can cause an increased endometrial thickness due to chronic anovulation and the effect of unopposed estrogens on the endometrium. Therefore, women with chronic anovulation have more chances to develop endometrial hyperplasia or even endometrial carcinoma. Endometrial carcinoma has been reported even at the age of 20 due to PCOS. Therefore, if a woman has a long-term amenorrhea (>6 months), even if the endometrial thickness is normal (5-12 mm) a biopsy is required for ruling out any endometrial pathology<sup>[21]</sup>. Apart from its thickness, the appearance of the endometrium in transvaginal ultrasound should be assessed. Peri *et al* found that a heterogeneous cystic endometrium is associated with the prolonged proliferative phase from chronic anovulation as well as endometrial hyperplasia<sup>[22]</sup>. Iatrakis *et al* also found in their study that both in women diagnosed as having insulin resistance without PCOS and in women with PCOS without insulin resistance, the thickness of the endometrium was relatively high and closer follow up of these patients is needed in order to detect those in risk to develop endometrial hyperplasia and/or atypia<sup>[23]</sup>.

#### Etiology of PCOS

The exact etiology of PCOS is not known but several factors probably play role for its development. Hyperinsulinemia thought to be one of the main underlying reasons. Women with PCOS develop insulin resistance so they need the production of more insulin from the pancreas in order to control a normal glucose levels. Hyperinsulinemia in turn cause increase androgen production and high testosterone level interfere with normal proliferation of the follicles and ovulation in general. Another etiologic factor for PCOS is a genetic predisposition. The familial clustering of hyperandrogenemia, anovulation and polycystic ovaries suggests an underlying genetic basis of the disease. The strong link between hyperinsulinemia and hyperandrogenism also suggests that the stimulatory effect of insulin on ovarian androgen production is influenced by a genetic predisposition. Studies of large families showed that there is an autosomal-dominant mode of inheritance of the disease. By this way clinicians should counsel families that theoretically 50% of mothers and sisters within a family can manifest PCOS<sup>[21]</sup>.

Interestingly, even if PCOS has a genetic basis, it is likely that not all women with the gene (or genes) will develop the disease. It is more likely to develop it if there is a family history of diabetes mellitus (especially type 2), or if there is a family history of early baldness (before the age of 30) in related men. So, in women who have these predisposing factors in their family, in order to somehow prevent the development of the PCOS, it is recommended to maintain a normal BMI throughout their lives.

#### Clinical features of PCOS

- Oligomenorrhea/amenorrhea.
- Infertility, first trimester miscarriage.
- Obesity.
- Hirsutism (chin, chest, upper abdomen, back, upper lip).
- Acne.
- Acanthosis nigricans.
- Alopecia.
- Asymptomatic (20% of the women with PCOS).

#### Risks of women with PCOS

Women having PCOS, depending on the severity of the syndrome, may have a higher risk than general population to develop diabetes mellitus, cardiovascular diseases, high blood pressure and endometrial cancer later in their lives<sup>[24]</sup>.

#### Differential Diagnosis

Pregnancy, hypothyroidism, hyperprolactinemia, ovarian tumor, adrenal tumor, adrenal hyperplasia, Cushing's Syndrome and simple obesity should be excluded and investigated.

#### Laboratory tests-results for PCOS

- Pregnancy test.
- LH/ FSH ratio >2.
- Decreased SHBG due to hyperinsulinemia which suppresses the production of SHBG (sex hormone binding globulin) from the liver.
- Increased free testosterone and D4 androstenedione.
- Prolactin normal or slightly elevated.
- T3, T4, TSH usually normal levels.
- Plasma insulin levels. Usually there is hyperinsulinemia.
- Determination of DHEAS (sulphate dihydroepiandrosterone), 17OH progesterone, if total and free testosterone abnormally elevated, in order to exclude the presence of adrenal hyperplasia or tumour.
- Increased Antimullerian hormone A.M.H.
- Additionally if we suspect Cushing's syndrome then we have to proceed

to 24 h urine free cortisol and dexamethasone suppression test.

- Performance of glucose tolerance test with 75 gr of sugar and measurement of levels of glucose and insulin at 0' and 120 min especially in obese women is mandatory (normal 2 h glucose < 140 mg/dl, normal 2 h insulin levels < 100 µU/ml)<sup>[21]</sup>.

#### Treatment

One of the most important issues in PCOS is to treat the irregular menses. Infrequent menstrual cycles carry a 3 fold increased risk of endometrial carcinoma. In general four menses per year are required to alleviate this risk. This could be accomplished by using the following therapeutic options:

1. Use of oral contraceptive pill. The type of the pill that we are going to use depends from the symptoms of the patient. In case of irregular periods without signs of hyperandrogenemia (hirsutism, oily skin with papules) then one choice is a pill with drospirenone: 20 µgr of ethinylestradiol + drospirenone or 30 µgr of ethinylestradiol + drospirenone. In women with signs of hyperandrogenemia we can use a pill with 35 µgr ethinylestradiol plus cyproterone acetate, pill which has a stronger antiandrogenic effect than the other pills due to the cyproterone acetate component. The use of 35 µgr ethinylestradiol plus cyproterone acetate carries a greater risk for the development of deep venous thrombosis so the therapy should not exceed the six months. After this period the woman can continue Yasminelle therapy as mentioned above.

2. Use of medroxyprogesterone 10 to 14 days every month in the luteal phase of each cycle in case where there is a relative contraindication for the use of combined oral contraceptive pill.

3. Lifestyle changes, weight loss and physical exercising. These changes showed improvement in menstrual function in 82% of patients with oligomenorrhea, who lost this way more than 5% of their initial body weight. By this way the insulin resistance is decreased restoring ovulation function.

4. The metformin use to restore normal menses especially to those patients who are obese and have an insulin resistance. According to Lord JM *et al* from the Cochrane Database



Systematic Review metformin is an effective treatment for anovulation in women with PCOS. Additionally their findings showed that ovulation rates are higher when metformin is combined with clomiphene (76% versus 46% when used alone). Also metformin has a significant effect in reducing fasting insulin levels, blood pressure and low density lipoprotein cholesterol (LDL) but there is no evidence of effect on body mass index or waist: hip ratio. Finally according to Sinawat S et al there are insufficient data to determine whether short course (less than four weeks) of metformin pre-treatment is as effective as the conventional long course (more than four weeks) before initiation of clomiphene citrate for ovulation induction<sup>[25,26]</sup>.

5. Use of progesterone coated coil can also reduce the risk of endometrial hyperplasia and cancer due to the topical effect of the progesterone on the endometrium<sup>[21,27]</sup>.

#### **5. Drugs that induce abnormal endometrial proliferation**

##### **Tamoxifen use in breast cancer**

Tamoxifen is used as adjuvant therapy for breast cancer. It belongs to the SERM family of drugs. It's a nonsteroidal triphenylethylene derivative with pure antiestrogenic effect on the breast but acts as estrogenic agonist on the endometrium. By this way it can cause hyperplasia or even cancer of the endometrium. A common sonographic pattern is the "Swiss-cheese" appearance of the endometrium but there is no clear cut-off for normal versus pathological endometrial thickness in these patients. The incidence of endometrial hyperplasia in postmenopausal women treated with tamoxifen for breast cancer is 1.3% to 20%. In microscopic examination of endometrial tissue of patients taking tamoxifen there is a diffused endometrial thickening with a characteristically fibrotic stroma with collagen bundles separating stromal cells. This microscopic picture can explain the difficulty in obtaining endometrial tissue during biopsy in cases with confirmed sonographic pathology. In a study by Cohen *et al* in 77 patients, with breast cancer who treated with tamoxifen, 76 women had thickened endometrium in TVS but in endometrial biopsy in only 23 (29%) of them the endometrial tissue was adequate<sup>[10]</sup>.

Tamoxifen use increases not only the risk of endometrial hyperplasia but also the risk of endometrial cancer. Most patients presented with abnormal vaginal bleeding. One large study by Fornader et al in 931 patients taking tamoxifen showed that the endometrial cancer risk was increased 6.4 times as compared with the control group. The Early Breast Cancer Trialists' Collaborative Group reported in trials involving one, two and nearly five years of tamoxifen treatment an endometrial cancer risk increased by 2.2%, 1.8% and 4.2%, respectively. All randomized tamoxifen trials in 1998 showed that the incidence of endometrial cancer was doubled in patients who took tamoxifen for one to two years and quadrupled in those who took the drug for five years<sup>[10,28]</sup>.

The parallel use of progesterone to reverse the tamoxifen effects on endometrium has not yet been proven effective. Additional studies are needed to investigate the use of progesterone coated IUDs (intrauterine devices) for this purpose.

It is important that once the endometrium has thickened with the use of tamoxifen, and this happens up to 54% (>5mm) of the patients, the examiner has to perform a hysteroscopy-controlled endometrial biopsy instead of a blind-controlled one. This is required since the specificity and sensitivity of transvaginal ultrasound is quite poor since the rate of false positive results is very high (46-56%). In tamoxifen-treated patients the ultrasound is valued for normal findings.

The American College of Obstetricians Gynecologists in 1996 set the following recommendations for the women with breast cancer treated with tamoxifen.

- Women with breast cancer should undergo annual gynecological examinations, including pap smear, bimanual and rectovaginal examinations.
- Any abnormal bleeding or discharge should be investigated by means of endometrial biopsy.
- Practitioners should be alert to the increased incidence of endometrial malignancy. Screening procedures or diagnostic tests should be performed at the discretion of the individual gynaecologist.
- If a woman develops tamoxifen-induced atypical endometrial hyper-

plasia, then hysterectomy should be considered if the therapy must continue

- Tamoxifen treatment may be reinstated after hysterectomy for endometrial carcinoma, following consultations with the physician responsible for the woman's breast care<sup>[10,28,29]</sup>.

Other guidelines for screening and following up tamoxifen-treated patients were suggested by Neven and Vergote following the agreements of the consensus meeting on tamoxifen and uterus (Brussels, 1997). They advise that the annual follow up with a transvaginal ultrasound should start in the third year of tamoxifen intake. The endometrial thickness and pattern need to be assessed. If it is below 5 mm and regular, then we can stand-by and monitor the patient; however if it exceeds 5 mm and has an irregular pattern then hysterosonography and or hysteroscopy with biopsy are indicated<sup>[30]</sup>.

Valenzano et al made an interesting observation on endometrial thickness of the women treated initially with tamoxifen and later with anastrozole. They found that in postmenopausal women with breast cancer anastrozole reverses the tamoxifen-induced increase of the endometrial thickness and sonographic endometrial cystic appearance. The main reduction of endometrial thickness was 4.5 mm<sup>[31]</sup>.

Another study by Kesim et al. showed that the use of levonorgestrel-releasing intrauterine system may prevent the increased risk of endometrial polyps and hyperplasia associated with the tamoxifen use in breast cancer women<sup>[32]</sup>.

##### **Hormone replacement therapy**

Modern HRT regimens contain both estrogen and progestin, given either in a cyclical or continuous combined manner in patients who haven't undergone hysterectomy. Irregular bleeding is less likely under sequential therapy than under continuous therapy. Unopposed estrogens can increase the risk of endometrial hyperplasia by approximately 20% and the relative risk of carcinoma is two to three times higher. This risk is dramatically reduced by the addition of progestogen to the regimen, but interestingly enough, cyclical progestogen as part of a sequential HRT regimen does not completely eliminate the risk of carcinoma<sup>[33,34]</sup>.

In a large study by Feeley *et al* the prevalence of endometrial hyperplasia associated with sequential HRT was 5.4% and that of atypical hyperplasia is 0.7%<sup>[35]</sup>. Continuous combined HRT was not associated with the development of hyperplasia or carcinoma and may normalize the endometrium of women who have developed complex hyperplasia on sequential

HRT. This type of HRT can actually act protectively against endometrial cancer and hyperplasia.

### Conclusion

Pathological endometrial thickening can be found in many diseases and can lead to endometrial cancer.

Endometrium investigations based on modern imaging and on new tools for

endometrial sampling for histology are routine-used and should be encouraged in gynecological practice in women at high risk or in those with pathological symptoms.

Moreover the very good prognosis for pre-malignant lesions and early-diagnosed endometrial cancer remind us that early diagnosis of endometrial pathology is very effective. ■

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