How to Prevent, Diagnose, and Treat Gynecological Cancer in PCO Patients?

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18.1 Introduction

Polycystic ovaries syndrome (PCOS) was first described in 1935 by Stein and Leventhal. Fourteen years later, an association between PCOS and endometrial cancer (EC) in young women was published by Speert [1]. When analyzing the risks of cancer in patients with micropolycystic ovaries, the most common is endometrial cancer. The meta-analysis of Haoula et al. in [2] includes five studies with a total of 4605 patients. Eighty-eight women had PCOS of whom 47 had EC and 4517 did not have PCOS of whom 773 had endometrial cancer. According to these results, women with PCOS are about three times more likely at risk to develop endometrial cancer (OR: 2.89). If analyzing results depending on the age, patients under the age of 50 would have an even greater risk. This translates into a 9% lifetime risk of EC in Caucasian women with PCOS compared with 3% in women without it. Although most women (91%) with PCOS will not develop endometrial cancer, this study has shown that they are at higher risk. The same year, Fauser et al. [3] confirmed that there were moderate quality data to support that women with PCOS have a 2.7-fold (95% CI 1.0–7.3) increased risk for EC (level B). Most EC are well differentiated and have a good prognosis. Limited data suggest that PCOs women are not at increased risk of ovarian cancer nor breast cancer (level B).

In [4], Barry et al., analyzing five studies comparing women with PCOS and non-PCOS, demonstrated that PCOS patients are at greater risk of presenting EC (OR = 2.79) and even greater if under the age of 54 (OR: 4.05). Compiling results from three comparative studies, no increased risk of ovarian cancer was found in women suffering from PCOS (OR 1,41). Subsequent analysis showed that women under the age of 54 had an increased OR of 2.52. However, this difference was

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found in a single study, and the authors concluded that no significant evidence showed an increased risk of ovarian cancer in PCOS patients.

Concerning the risk of breast cancer, it was evaluated in three comparative studies, and no significant differences could be shown whether analyzing the entire group population (OR 0.95) or the less than 54 years patients group (OR 0.78).

Concerning the other gynecological cancers, there is insufficient evidence to evaluate any association between PCOS and vaginal cancer, vulvar cancer, cervical cancer, and uterine leiomyosarcoma.

18.2 Endometrial Cancer Overview

Endometrial cancer is the most common gynecological cancer in North American and European women. It's the fourth most common cancer in women, 319,500 cases and 76,000 deaths being reported worldwide annually. The incidence rate has increased by ± 50% in Europe since the early 1990s. The EC is predominant in postmenopausal women as the peak incidence is observed between 50 and 60 years. Concerning the histological classification two types of EC are described, the type 1 endometrioid representing 80–90% of all EC. Type 1 EC is estrogen-induced, has a good prognosis, and is associated to PCOS. A pre-invasive status with an atypical hyperplasia is described. On the contrary, type 2 EC (serous, clear cell, mucinous) is estrogen-independent and of poor prognosis.

Clinical presentation of EC is usually the presence of AUB which allows the diagnosis at an early stage. The prognosis is related to the histology and to the stage. The estimated overall 5-year survival rate is 81.5% and 97.6% in cases of well-localized endometrioid EC [5]. Risk factors for developing EC include PCOS, obesity, nulliparity, type-2 diabetes, insulin resistance, tamoxifen use, and exposure to unopposed estrogen therapy.

18.3 Etiological and Molecular Mechanisms

The understanding of molecular mechanisms is needed to develop clinical strategies to prevent EC in PCOS. The type 1 EC is explained by an imbalance between estrogen and progesterone. The cumulative exposure to estrogen is higher in case of early menarche, late menopause, or nulliparity. The estrogen is increased for the age in postmenopausal obesity. In PCOS, there is an insufficient progesterone secretion due to a chronic anovulation leading to a prolonged endometrial exposure to unopposed estrogen. The latter promotes endometrial growth and proliferation with a higher probability of random mutations in oncogenes and tumor suppressor genes.

The World Health Organization (WHO) and the International Society of Gynecological Pathologists (ISGP) established a pathological classification of atypical endometrial hyperplasia (EH). The simple EH is similar to a normal proliferative endometrium with an abnormal glandular growth despite the presence of a normal gland-to-stroma ratio. The complex EH is characterized by an increased

complexity in the glandular architecture, with glandular proliferation and a consequent disproportion in the gland-to-stroma ratio, with the former increasing relative to the latter. The presence of cytological atypia identifies the third and fourth categories: simple atypical EH and complex atypical EH.

Yang et al. [6] developed an interesting animal model to understand the link between endometrial hyperplasia (EH), endometrial cancer, and hormonal stimulation. They induced EH in a mouse model with a subcutaneous estradiol-sustained releasing pellet. The authors were able to demonstrate the assessment of local and systemic hormone effects after 2, 4, 6, 8, and 10 weeks post-E2 stimulation and the evolution towards EC.

Four weeks after the implantation of E2 pellets, disordered proliferative endometrium was observed, non-atypical hyperplasia after 6 weeks, localized atypical endometrial hyperplasia after 8 weeks, and diffuse atypical hyperplasia after 10 weeks. The expression of hormone receptors was found to be altered as EH progressed to atypical hyperplasia. An increase in nuclear PR expression was noted after E2 expression, but a total loss in PR occurred in some endometrial glands when simple EH was observed. The expression of nuclear ER was found to be reduced in disordered proliferation but increased when EH progressed to atypical EH. This animal model, easily reproducible, could be used for testing therapeutic agents to investigate and to improve the management of EH which remains a serious health problem.

Insulin resistance reduces receptor binding and decreases insulin receptor-mediated transduction. This leads to a hyperinsulinemia which causes an inhibition in the liver of sex hormone binding globulin (SHBG) secretion. This decrease of SHBG reduces the production of insulin growth factor binding protein (IGFBP) which causes exaggerated bioactivity of insulin growth factors (IGF). All these mechanisms promote the ovarian steroidogenesis and the androgen production in theca cells.

PCOS women are often obese, and it has been demonstrated that obesity is strongly related to endometrial carcinoma risk [7]. Of all obesity-related cancers occurring among women, higher body mass index (BMI) is most strongly related to EC risk. The obese women have a two- to five-fold elevated risk of EC. This applies to both menopausal and premenopausal patients. The relative risk of EC is 1.59 times higher for each 5 kg/m^2 increase in BMI [8]. Each 5 kg increase in adult weight gain was associated with a 39% increase in postmenopausal EC risk among non-users of menopausal hormones.

Different hypotheses have been suggested. First, postmenopausal obesity is associated with an increased circulating estrogens rate due to aromatization of androgens in adipose tissue and to higher levels of bioavailable estrogen because of decreased SHBG levels. Premenopausal obesity may lead to a higher frequency of anovulatory cycles and relative progesterone deficiency when compared to the high estrogen levels. Second, the obesity contributes to insulin resistance and vice versa. Finally, obesity also induces non-hormonal modifications such as inflammation, immune dysfunction, and cell signaling pathway errors contributing to an increased risk of endometrial cancer [5].

18.4 Prevention of Endometrial Cancer

The perfect prevention for endometrial hyperplasia and endometrial cancer is not known. The recommendations established in 2018 by the international evidence-based guideline for the assessment and management of PCOS claimed that "The health professionals and women with PCOS should be aware of a 2- to 6- fold increase risk of endometrial cancer, which often presents before menopause; however, absolute risk of endometrial cancer remains relatively low. The health professionals require a low threshold for investigation of endometrial cancer in women with PCOS or a history of PCOS, with investigation by transvaginal ultrasound and/or endometrial biopsy recommended with persistent thickened endometrium and/or risk factors including prolonged amenorrhea, abnormal vaginal bleeding or excess weight. However, routine ultrasound screening of endometrial thickness in PCOS is not recommended."

18.5 Place of Hormonal Prevention

A pragmatic approach could include combined oral contraceptive (COC) or progestin therapy in patients with cycles longer that 90 days [9].

Progestins inhibit proliferative pathways by modulation of endometrial glands' secretory differentiation, inhibition of estrogen receptor function, and endometrial cell mitosis. Progestins are pro-apoptotic and also anti-angiogenic thanks to a stimulation of stromal insulin-like growth factor binding protein-1 (IGFBP-1), which inhibits insulin-like growth factor-1 (IGF-1) expression and activity. This is significant as IGF-1 is proliferative and anti-apoptotic, with increased expression in EH [10].

According to the ESHRE recommendations, specific types or dose of progestins, estrogens, or combination of COC cannot be suggested in adults and adolescents with PCOS. The 35-microgram ethinylestradiol plus cyproterone acetate preparation should not be considered as first-line therapy in PCOS, due to adverse effects such as venous thromboembolic risks (especially in overweight women).

Nevertheless, it is well-known that the women with PCOS taking COC daily for 21 days per month reduce by 50% the risk of EC compared with non-users. The risk reduction is observed after at least 1 year of use. The increasing duration of COC use is significantly related to a greater protection, and this risk reduction after discontinuation is persisting for up to 20 years [5]. Furthermore, COC is associated with a reduction risk of ovarian cancer in all women [11]. The risk reduction is about 20% for every 5 years of COC use. A reduction of 50% occurs after 15 years of use. The benefit is already observed after 1 year of use and remains significant after discontinuation. Other contraceptive methods like injectable contraceptive, implant, or transdermal patch need more studies to be evaluated.

A decrease of the combined postmenopausal hormone therapy use was observed in the United States [12] after the initial women's health initiative (WHI) report in 2002 [13]. This decrease was followed by an endometrial cancer increase, which can be attributed to this hormone therapy decrease. In [14], Chlebowski et al.

evaluated the effect of continuous combined estrogen plus progestin on EC in the WHI randomized trial. Women aged 50–79 years old with normal endometrial biopsy at entry were randomly assigned to once – daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate (n = 8506) as a single pill or matching placebo (n = 8102).

They observed that the use of continuous combined estrogen plus progestin for 5.6 years in postmenopausal women with normal endometrial biopsy at entry of the therapy resulted in a statistically significant reduction in endometrial cancer incidence [15]. Indeed, the continuous estrogen plus progestin use is associated to a 35% lower endometrial cancer risk compared to non-users. The greatest risk reduction occurred among obese women.

The progestin dose, schedule, and duration have to be taken into consideration in the prevention of EC. Indeed, sequential regimens with fewer days of progestin exposure are less effective in reducing endometrial cancer risk. In 2014, Briton and Felix [16] studied the effect of various hormonal regimens on the risk of developing EC. The data revealed that the use of estrogen plus sequential progestin for less than 10 days per month was linked to a higher risk of EC (OR = 1.32, 95% CI = 1.06 to 1.65), while the progestin sequential use for 10–14 days didn't have an impact, positive nor negative (0R = 1.32, 95% CI = 0.84 to 1.3). The addition of micronized progesterone to estrogen is less associated to breast cancer in some studies. However, the latter association provides few to no protection against EC (HR = 2.42 95% CI = 1.53 to 3.83).

Taking into account that progestogenic potency varies as normethyltestosterone derivatives are more potent on the endometrium than pregnane and micronized progesterone, rules for optimal endometrial protection have been published by Gompel in [17] as follows:

1. Adapt the dose of progestogen to dose/duration of estrogen treatment.
2. Inform the woman of the importance of taking the progestogen pill.
3. Check regularly woman's compliance on the progestogen.
4. Adapt the dose to body mass index.
5. Prefer continuous treatment rather than sequential.

18.5.1 Place of Weight Control

It has been clearly demonstrated that obesity has a linear relationship with all cancer types [7]. As obesity and an increased BMI are strongly associated with the incidence and mortality of endometrial cancer, the weight control is very important in the prevention of EC. A moderate physical activity is associated with 20–30% reduction in EC risk. An increase of 1 h a week in physical activity is related to a 5% lower risk of EC. The benefits of physical activity are multiple: weight control, increase in SHBG levels leading to less bioavailable estrogen, decrease of inflammation, reducing adipose storages, improving insulin sensitivity, and also immune function.

18.5.2 Place of Metformin

Metabolic syndrome, a triad including obesity, hyperinsulinemia, and diabetes, is commonly observed in PCOS women and seems to be the key mechanism of EC pathogenesis. Metformin is an insulin sensitizer agent and could have a chemoprotective, anti-proliferative effect and could also increase the expression of progesterone receptor.

Metformin directly activates adenosine monophosphate (AMP)-activated protein kinase (AMPK) via oxidative phosphorylation inhibition which reduces adenosine triphosphate (ATP). Metformin also promotes AMPK activation by liver kinase B1 (LBKI), and murine models have shown that this AMPK activation inhibits cancer incidence [18].

Metformin is safe, widely available, licensed for type-2 diabetes and may help to lose weight. It has been shown to be of value in reversing endometrial hyperplasia in both animal and human studies and could therefore be used to prevent EC in PCOS. In [19], Shafiee et al. summarized the literature and identified only three human studies including five patients with regression of atypical endometrial hyperplasia. According to the Cochrane Database of Systematic Reviews of [20], there is no evidence to support or not the use of Metformin alone or in association with progestins for the treatment of EH.

18.6 Diagnosis of Endometrial Hyperplasia and Cancer

The average age at diagnosis is 62 years with a peak of incidence from 50 to 60 years of age. AUB is the cardinal symptom in peri- or postmenopausal women. The diagnosis can also be made on cervical cytology or can be an incidental finding on imaging (transvaginal ultrasound, TVUS).

TVUS is the first-line imaging modality used to examine clinical cases considered suspicious for endometrial hyperplasia. There is a high sensitivity in the measurement of endometrial thickness in the longitudinal plane of the scan. The thresholds used are the following: 4 mm in postmenopausal women and 12 mm in childbearing age women. Indeed, in postmenopausal women an endometrial thickness of more than 4 mm has an 85% positive predictive value for endometrial anomalies, with 96% of specificity and 100% of sensitivity [5].

In [21], Park et al. established predictable clinical factors for endometrial disease in women with PCOS. As described earlier, endometrial disease includes several stages of evolution: simple hyperplasia, complex hyperplasia (with or without cytologic atypia), and adenocarcinoma. This study performed in a series of 117 women with PCOS demonstrated that in predicting endometrial disease, an endometrial thickness >8.5 mm has a 77.8% sensitivity and 56.7% specificity. Moreover, age >25.5 years has a 70.4% sensitivity and 55.6% specificity. It is important to note that in their series the incidence of endometrial disease was as high as 23.1%, including EH in 21.4% and EC in 1.7% of cases.

Office hysteroscopy is a very good method to evaluate the endometrium with a direct view of the cavity and the possibility of performing biopsies. The no-touch procedure makes examination more comfortable for patients. The principal morphological criteria serving as hysteroscopic predictors of endometrial hyperplasia (78% of sensitivity) are inhomogeneous polypoid or papillary endometrial thickening (focal or diffuse), abnormal vascular patterns, and presence of glandular cysts or glandular outlets demonstrating abnormal architectural features (thickening, irregular gland density, dilatation). It should be noted that these criteria have not been defined based on scientific evidence resulting from controlled randomized clinical trials, but rather stem from retrospective trials published between 1987 and 1996 [22]. Each of the following hysteroscopic criteria can reasonably be linked to an endometrial hyperplasia context. However, taken individually, each of them is entirely unspecific. Some specific hysteroscopic features suggestive of an endometrial malignancy are also described: whitish or green-gray coloration, areas of necrosis, hemorrhage and microcalcifications, atypical vascularization, irregular or ulcerated surface, and soft consistency (Figs. 18.1 and 18.2).

Endometrial biopsy performed during office hysteroscopy or operative hysteroscopy is required if a woman has persistent post-menopausal bleeding or abnormal menstrual bleeding regardless the endometrial thickness.

Specifically, in women at high risk of developing EC, such as Lynch syndrome or Cowden disease, the screening is recommended at 30 years old by evaluating the endometrial thickness by TVUS and also by performing an endometrial biopsy [5].

Very recently, the risk factors for EC or EH in adolescents and women 25 years old or younger have been described, demonstrating that PCOS was frequently associated to endometrial pathologies such as complex EH with or without atypia and also EC. This study pointed out the importance of endometrial evaluation in young patients suffering from abnormal uterine bleeding [23].

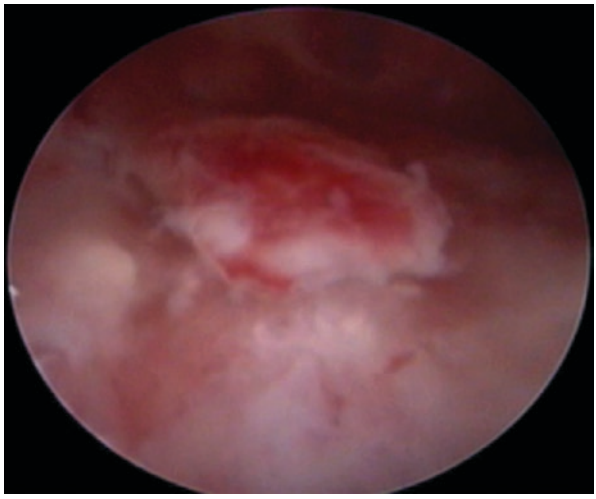

Fig. 18.1 Office hysteroscopy: simple endometrial hyperplasia

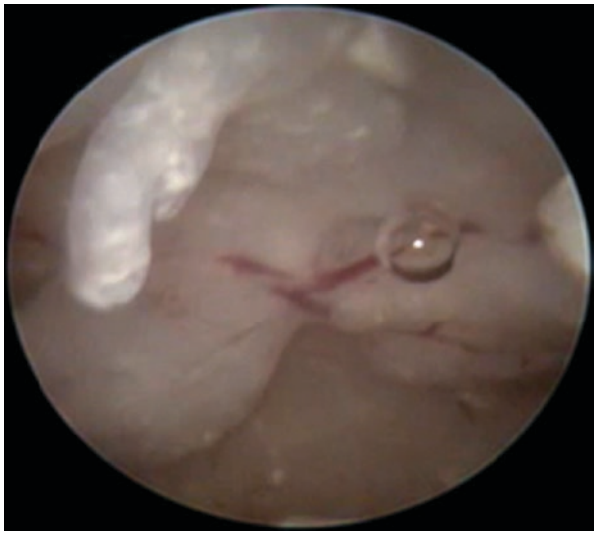

Fig. 18.2 Office hysteroscopy: endometrioid tumor grade III

18.7 Risk of Progression of Endometrial Hyperplasia

The risk of progression of simple EH is low as 80% of cases will regress spontaneously. Simple EH is associated with 3% rate of progression to complex EH and 8% to simple atypical EH. The risk of progression of atypical EH to EC is estimated at 52% [24].

18.8 Treatment of Endometrial Hyperplasia and Cancer

18.8.1 Endometrial Hyperplasia

The treatment options for EH depend on patient's age, the presence of cytological atypia, and the desire of pregnancy. EH without atypia responds well to several progestins such as medroxyprogesterone acetate, megestrol acetate, levonorgestrel, and norethisterone acetate. A systematic review and meta-analysis of RCT comparing the administration of oral progestins versus the levonorgestrel-releasing intrauterine system for non- atypical EH demonstrated better therapeutic effects of LNG-IUS at 3, 6, 12, and 24 months [25].

Surgical procedures are favored in cases of EH with atypia especially if there is no desire of fertility. Conservative treatment by using endometrial ablation is possible only in simple and complex non-atypical EH. If atypical EH is diagnosed in postmenopausal women, hysterectomy with concomitant bilateral salpingo-oophorectomy is recommended.

18.8.2 Endometrial Cancer

The current standard management of endometrial cancer is surgery with total hysterectomy with or without oophorectomy. Depending on the stage of the disease, radical hysterectomy will be performed (total hysterectomy with a pelvic and paraaortic lymphadenectomy). If there is an advanced pathologic stage, an adjuvant therapy is needed with radiation, vaginal brachytherapy, and/or chemotherapy.

The steady increase in EC cases among young women of reproductive age means that a nonsurgical management is needed. A fertility-sparing therapy is possible with oral progestins or levonorgestrel-releasing intrauterine system. The fertility-sparing therapy was studied [26] with 34 observational studies involving 408 patients with early clinical stage and well-differentiated EC (group 1) and 141 patients with atypical complex EH (group 2). The pooled regression rate was 76.2% in the group 1 and 85.6% in the group 2. The relapse rate was 40.6% in the group 1 and 26% in the group 2. The live birth rate was 28% in the group 1 and 26.3% in the group 2. During the follow-up, 3 to 4% of ovarian malignancies (concurrent or metastatic) have been diagnosed. A progression of disease to higher than stage 1 has been observed in 2% and 2 deaths have been reported. For the group 2, the regression has been better with the LNG-IUS than with the oral progestagens. This systematic review and meta-analysis established essential conditions for the successful completion of this treatment. The duration of the treatment must be at least 3 months and up to 12 months [27, 28]. A repeat biopsy is needed to confirm the regression before a pregnancy. To obtain pregnancy, it is recommended to undertake assisted reproduction treatment in order to maximize the chances and to avoid the prolonged unopposed estrogen period and to minimize the delay for performing hysterectomy. The recommendations are to undergo staging hysterectomy with bilateral salpingo-oophorectomy once the family is complete. The follow-up must last at least 5 years and the risk of relapse should not be underestimated.

18.9 Conclusion

Women with PCOS will about three times more likely develop endometrial cancer, and patients under the age of 50 are at even greater risk. It is difficult to separate the effects of PCOS from its component factors such as obesity and insulin resistance. The prevention consists of COC, progestin or IUD, and hormonal therapy after menopause. There is also a very important role of weight loss and maybe of Metformin. Facing a patient suffering from PCOS, even if it is a young patient, the health professionals should not hesitate to do an endometrial evaluation by transvaginal ultrasound and a biopsy especially if there is a complaint of abnormal uterine bleeding.

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