Chapter 9

Endometrial Cancer Prevention with Levonorgestrel-Releasing Intrauterine System

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1. Introduction

Endometrial cancer is a potentially preventable disease but still many new cases occur each year. In the USA, the incidence of endometrial cancer has increased by more than 30% over the past 20 years. [1] Globally, about 4% of all cancers in women are endometrial cancers that occur predominantly in postmenopausal women, although many are now also diagnosed in younger women. [2] It is the leading gynecological malignancy with approximately 47,130 women diagnosed in 2012 in the USA. [3] Endometrial cancer is often diagnosed at an early stage due to abnormal vaginal bleeding which occurs as a prominent clinical feature in most women. Two types of endometrial cancer can be distinguished. Type 1, occurring in approximately 80% of women, carries a better prognosis, has predominantly endometrioid histology and is well or moderately differentiated (grading G1-G2), and Type 2 includes worse prognosis, poorly differentiated (grade G3) carcinomas, like serous and clear cell carcinomas. [4] The epidemiology of Type 1 endometrial cancer is fairly well understood: 1) prolonged unopposed estrogen exposure is the endocrine background of this hormonally regulated neoplasm; 2) hereditary factors are associated with an increased risk and high parity and later age at last birth are protective [5, 6]; 3) the role of obesity as an important risk factor is well established; 4) combined oral contraceptives are protective, whereas 5) hormone replacement therapy (HRT) in the menopause is an important risk factor and the risk increases markedly with the use of estrogen only and sequential HRT. Understanding the causative role of these conditions constitutes the basis for prevention strategies. The rising obesity epidemic and decreased fertility are likely to result in a higher incidence of endometrial cancer and may become an important public health problem globally in the coming years. This communication will focus on the risk groups and will formulate some strategies for the prevention of cancer of the endometrium in women at increased risk.

2. Risk factors for endometrial cancer

2.1. Hormone replacement therapy

The primary role of progestin in postmenopausal estrogen therapy is endometrial protection to prevent hyperplasia. [7] Prior to the widespread use of combined estrogen-progestin therapy (EPT), the risk of developing hyperplasia due to unopposed estrogen stimulation was substantial. Endometrial hyperplasia in postmenopausal women with an intact uterus, treated with unopposed oral estrogen, was found in 20% of women during the first year and in 62% after 3 years of estrogen therapy (ET). [8] In support of this finding, in the Postmenoapausal Estrogen/Progestin Intervention Trial, 62% of women who received only estrogen (0.625 mg of conjugated equine estrogen orally daily) developed endometrial hyperplasia. One third of these women had complex hyperplasia with or without atypia. [9] Hyperplasia is characterized by a proliferation of the endometrial glands. In non-atypical hyperplasia, the glands are outgrown yet normal, but in atypical hyperplasia glandular abnormality is already present both structurally and at cellular level. [10] Non-atypical hyperplasia rarely progresses to more severe conditions. Atypical adenomatous hyperplasia, on the other hand, has been observed to progress to adenocarcinoma of the uterus in 29% of cases. [11]

Progestins should, therefore, be added to ET in all postmenopausal women with an intact uterus. Since the mid-1980s, EPT has increasingly been prescribed. The North American Menopause Society reviewed the types of EPT regimen used in the USA and concluded that standard regimens provide adequate endometrial protection. [7] A Cochrane review devoted to this subject also came to the conclusion that the addition of an oral progestin to ET, administered either continuous cyclic or continuous combined, is associated with reduced rates of hyperplasia. [12] An important drawback of postmenopausal EPT is the occurrence of withdrawal or breakthrough bleedings. Withdrawal uterine bleedings occur in 80% of women using cyclic EPT. Continuous combined regimens avoid withdrawal bleeding, but breakthrough bleeding has been observed in up to 40% of women during the first 6 months. Most postmenopausal women dislike breakthrough bleedings and this is the most common reason for discontinuation and non-adherence to the treatment regimen. With EPT, therefore, irregular bleeding should be kept to a minimum. Depending on the EPT type, dose and route of administration, progestins may have adverse effects on the cardiovascular system, coagulation and breast tissue. The Women's Health Initiative (WHI) reported an increased risk for heart disease, stroke and breast cancer. [13] Since these adverse effects were not observed with ET alone, it is speculated that adding progestins may diminish the beneficial effects on atherosclerosis, vasodilatation and plasma lipids and may contribute to the increased risk of breast cancer. Indeed, the WHI study suggests that EPT may stimulate breast cancer growth and hinder breast cancer diagnosis due to increased mammographic density when a progestin is added to ET. [14, 15] This was confirmed in the Million Women Study and other studies, in particular a Swedish cohort study. [16, 17, 18]

Intrauterine-administered progestin, such as levonorgestrel (LNG), delivered directly to the target cells of the endometrium, has a profound suppressive effect on endometrial growth rendering the endometrium inactive and simultaneously eliminating uterine bleeding. [19,

20] Pharmacokinetic studies with an intrauterine system (IUS) releasing 20 μg of LNG/day (Mirena®; Bayer AG, Germany) have shown substantially lower plasma LNG concentrations than those seen with a subdermal LNG implant (Norplant®; Pfizer Pharmaceuticals Inc, USA), the combined oral contraceptive pill and the mini-pill; moreover, unlike with oral contraceptives, LNG levels with the Mirena LNG-IUS do not display peaks and troughs. [21] This is important because the low plasma levels may have a significantly lower impact on organs and tissues, such as the breast, coagulation system, and cardiovascular system.

Studies conducted by us and by others using continuous combined estrogen plus low-dose LNG-IUS after 5 years of use in postmenopausal women, provided data on the endometrial morphology to verify endometrial safety. The main objective of these studies was to evaluate an alternative route of progestin administration in postmenopausal women using ET. They suggest that continuous combined ET with intrauterine delivery of a progestin was highly accepted by the participating women. The rationale of the development of LNG-IUSs specifically for postmenopausal women is to minimize the potential adverse systemic effects. As progestins are required only to oppose the stimulating effects of estrogens on the endometrium, locally acting progestins, by definition, could avoid these unwanted metabolic effects. Intrauterine LNG delivery with low-dose systems, even though minimal absorption may occur, should be regarded as essentially locally acting. This regimen also offers important additional benefits that could be exploited, such as high adherence to treatment and a low discontinuation rate because of bleeding problems and progestin-like side effects. In addition, a LNG-IUS that adapts to the decreasing dimensions of the uterus gradually reduced in size due to the suppressive effect of LNG and the decreasing levels of endogenous estrogen, will be optimally tolerated by the women. [22, 23]

2.2. Polycystic ovary syndrome

Women with polycystic ovary syndrome (PCOS) are about three times more likely to develop endometrial cancer compared with women without this condition. [24] PCOS affects approximately 5 to 10% of women of reproductive age. The disorder is characterized by a disruption of normal reproductive physiology and should be diagnosed in women with oligomenorrhea or amenoorrhea, hyperandrogenemia and polycystic ovaries defined by ultrasonography after exclusion of medical conditions that cause irregular menstrual cycles and androgen excess. [25] Women with PCOS have a higher prevalence of obesity, impaired glucose tolerance and type 2 diabetes. They are at risk of cardiovascular disease and often have features of metabolic syndrome, including hypertension, dyslipidemia, visceral obesity and insulin resistence. [26] Women with PCOS should, therefore, be screened for type 2 diabetes and for cardiovascular risk by fasting glucose followed by a glucose tolerance test, BMI, fasting lipid and lipoprotein levels, and other metabolic syndrome risk factors. The condition that makes PCOS patients vulnerable to endometrial cancer is chronic anovulation as prolonged exposure to unopposed estrogen can lead to endometrial hyperplasia and cancer. It is important to identify individuals at risk at an early stage.

From 2 to 14% of patients diagnosed with endometrial cancer are women younger than 40 and the diagnosis is typically associated with the detection of an accompanying hyperestrogenic

state. [25] According to studies in the United States, an estimated prevalence in very young women is 0.8%. [27, 28] A comprehensive review of PCOS was published by the American College of Obstetricians and Gynecologists. [29] Of note, PCOS can occur both in normal weight and overweight women. Yet classically, the young woman with endometrial hyperplasia or cancer is obese and nulliparous but, recently, several studies found up to 50% of women with endometrial cancer to be slender and with regular menstrual cycles. The proportion of estrogen and progesterone receptor positivity is similar in both obese and slim patients. Such women should be evaluated for concurrent ovarian malignancy (see Lynch syndrome below) which occurs in some studies in approximately 10% of cases. Therefore, 3-D ultrasound and magnetic resonance imaging (MRI) can be valuable additions in the diagnosis and staging of these patients.

2.3. Excessive body mass: Overweight and obesity

Obesity has become a major public health problem on a global scale. Overweight and obesity are not only an established risk factor for cardiovascular disease and type 2 diabetes; they are also an important risk factor for the development of endometrial cancer. [30] Renehan at al. found that each increase in BMI of 5 kg/m^2 significantly increased a woman's risk for the development of endometrial cancer. [31] Estrogen is a known endometrial growth factor in these women. The excess estrogens originate mostly from the conversion of androstenedione to estrone and testosterone to estradiol by peripheral adipose tissue. [32] Consequently, in obese postmenopausal women, adipose tissue becomes the primary source of circulating estrogen. Concentrations of estrogens in the adipose tissue have been measured at levels several-fold above that observed in plasma. Also, higher levels of insulin in obese women contribute to the increased risk for endometrial cancer as insulin demonstrates mitotic and antiapoptotic activity. Furthermore, serum sex hormone-binding globulin (SHBG) levels decrease with increasing adiposity, thus rising the fraction of circulating unbound estrogen.

The relationship between obesity and endometrial cancer has been well studied and has been acknowledged as a risk factor in women over 30 years of age. A strong association between early age at diagnosis and Type 1 endometrial cancer was found. The relationship was linear, suggesting that as obesity becomes more severe, the underlying carcinogenic mechanisms are more vividly activated. [4] There is limited public knowledge of the relationship between obesity and cancer risk. Making the data available to overweight and obese women could be useful to inform them about the risks which could affect their lives at an early age, and about the steps they could undertake to reduce or eliminate this risk, since prevention and other risk reduction strategies in the obese/overweight female population are possible with a high degree of success.

2.4. Lynch syndrome

Lynch syndrome is one of the most common cancer predisposition syndromes estimated to affect as many as 1 in 370 individuals. [33, 34] Often called hereditary nonpolyposis colorectal cancer it is an inherited disorder that increases the risk of many types of cancer, particularly

cancers of the colon and rectum, which are collectively referred to as colorectal cancer. Individuals with Lynch syndrome also have an increased risk for cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin. Additionally, women with this disorder have a high risk for cancer of the ovaries and endometrium. Patients with Lynch syndrome may occasionally have noncancerous polyps in the colon. For many women with Lynch syndrome, the risk for endometrial cancer is comparable or even exceeds their risk for colorectal cancer. In the United States, about 140,000 new cases of colorectal cancer are diagnosed each year. Approximately 3 to 5 percent of these cancers are caused by Lynch syndrome. Estimates suggest that as many as 1 in 10 young age (< 50) endometrial cancers are associated with Lynch syndrome. Broader knowledge of population carrier frequency for DNA mismatch repair gene mutations could contribute to the understanding of the burden of cancer due to genetic susceptibility, but robust prevalence estimates are lacking. The lifetime endometrial cancer risk is between 27% and 71% which exceeds that of colorectal cancer. Mean age of occurrence is approximately 50 years (62 years in non-Lynch) and 18% are diagnosed under the age of 40 years. Practical guidelines for Lynch syndrome and early detection can be found via website: http://ghr.nlm.nih.gov/condition/lynch-syndrome. We are of opinion that women diagnosed with Lynch syndrome should be counseled on and consider the prophylactic long-term use of a LNG-IUS in relation to their increased endometrial cancer risk.

2.5. Tamoxifen adjuvant treatment for breast cancer

The long-term recurrence and mortality rates of breast cancer have been substantially reduced due to adjuvant treatment with tamoxifen. Tamoxifen is a selective estrogen receptor modulator (see Table 1) which exerts an anti-estrogenic effect on mammary tissue. [35] However, it also induces endometrial proliferation and women using tamoxifen harbor significantly more endometrial polyps than other women of which up to 36% could have hyperplasia or cancer. [36] The prophylactic use of LNG-IUS in women with breast cancer treated with tamoxifen is still controversial as the effect of the progestin released from the device on breast cancer recurrence remains uncertain notwithstanding the significantly reduced incidence of endometrial polyps. [37] Nonetheless, in the future, this situation could be clarified by the advent of an intrauterine system impregnated with a selective progesterone receptor modulator (SPRM; see Table 2) that would demonstrate powerful progestin action on the endometrium without any stimulatory, if not purely inhibitory, properties with regards to hormonally sensitive breast glandular tissue.

Compound	Commercial name(s)	Principal indication(s)
Clomiphene	Clomid, Clomifen	Ovulation induction
Tamoxifen	Tamoxiphene, Nolvadex	Breast cancer
Raloxifene	Evista	Breast cancer, osteoporosis
DT56a	Femarelle, Tofupill	Menopause, osteoporosis

Table 1. Examples of selective estrogen receptor modulators, or SERMs, for the use in the clinical setting.

Compound	Commercial names	Principal indications
Ulipristal	Ella, ellaOne, Esmya	Emergency contraception, uterine leiomyomas
Asoprisnil (J867)	Investigational - no commercial name given	Uterine leiomyomas, endometriosis
Telapristone (CDB-4124)	Investigational - bears names: Progenta, Proellex	Uterine leiomyomas, endometriosis

Table 2. Examples of selective progesterone receptor modulators, or SPRMs, for the use in the clinical setting.

3. Biology of progesterone and progestins

The endometrium is highly sensitive to sex steroid hormones. Estrogens cause endometrial proliferation and progesterone inhibits this growth by converting the endometrium to its secretory stage to prepare the uterus for implantation. In relation to endometrial protection, progesterone is the key inhibitor of carcinogenesis. The balance between the estrogen and progesterone activity during the menstrual cycle must be precisely maintained as an increase in the estrogen activity and/or a reduction in the antagonistic activity by progesterone will stimulate carcinogenesis. Estrogens act upon the endometrium through estrogen receptors (ERs), resulting in the induction of growth factors such as the epidermal growth factor, insulin-like growth factor-1 and growth-enhancing protooncogenes c-fos and c-myc. Besides these genomic effects of estrogens in the endometrium, estrogens exert nongenomic effects via activation of the PI3K/Akt prosurvival signaling pathway. Progesterone acts by binding to progesterone receptors (PRs), thus regulating multiple signaling pathways through PR-dependent transcriptional activity. In addition to ligand-mediated regulation, PR activity is also modulated by a variety of factors including microRNAs and epigenetic factors. [38] Despite their high degree of sequence identity, the PR isoforms maintain a number of unique biological functions, including: differences in transcriptional activity, ligand response, gene regulation, and tissue-specific physiological effects. [39] Unbeneficial role of some progestins is highlighted by the finding that medroxyprogesterone acetate, a widely used and quite powerful progestin, stimulates vascular thrombin receptor *in vitro*, thus being capable of triggering thromboembolic events. [40, 41]

4. Biology of progesterone receptor antagonists — Potentially stronger acting compounds?

Following the discovery of the antiprogestin mifepristone, hundreds of similar compounds have been synthesized, which can be grouped in a large family of PR ligands. This family includes pure agonists, such as progesterone itself and progestins, and, at the other end of the biological spectrum, pure progesterone antagonists (PAs). An intermediate position of the

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spectrum is occupied by SPRMs which demonstrate mixed agonist–antagonist properties. These compounds have numerous applications in healthcare of women.

Most PAs and SPRMs display direct antiproliferative effects in the endometrium when given orally, although with variable strength being compound- and dose-dependent. PAs can also be released using an IUS and induce endometrial atrophy in nonhuman primates. PAs and SPRMs have two important effects in primates: 1) they suppress endometrial growth by blocking the action of progesterone on endometrial progestational development and consequently induce amenorrhea; and 2) they suppress the proliferative effects of estrogen on endometrial proliferation and prevent unopposed action on this tissue. [42] These properties indicate the potential for clinical applications of these compounds which cover a broad field and are very promising in major public health areas. These include emergency contraception, long-term estrogen-free contraception (administered alone, or in association with a progestin-only pill to improve bleeding patterns), uterine leiomyomas (where they induce a marked reduction in tumor volume and produce amenorrhea) and endometriosis. Further developments might also include the treatment of hormone-dependent tumors. [43, 44]

5. Rationale for prevention using levonorgestrel-releasing intrauterine system

The first beneficial results with frameless FibroPlant® (Contrel Research, Ghent, Belgium) LNG-IUS in women with non-atypical and atypical endometrial hyperplasia were published in 2003. [45] Later, several reports followed using the framed Femilis® (Contrel Research) LNG-IUS and included two cases of endometrial carcinoma, all successfully managed. [46, 47] No failures occurred during follow-up for many years. The numbers were small but indicative of the extraordinary impact of LNG to suppress the hyperplastic and atypical endometrium.

The risk of developing cancer in women with atypical endometrial hyperplasia untreated for 20 years is between 8.6 and 42.5%. [48] In contrast, less than 5% of women with nonatypical endometrial hyperplasia will experience progression to carcinoma. The lower risk for women with nonatypical than atypical hyperplasia can assist in decision making for nonsurgical management of endometrial hyperplasia. The higher risks with atypical hyperplasia progressing to carcinoma warrant consideration of appropriate approaches as concurrent carcinoma among patients with atypical endometrial hyperplasia can range from 17 to 52% across studies. [49]

The standard treatment for endometrial hyperplasia with atypia or early stage (pT1a) adenocarcinoma of the endometrium is staging hysterectomy with bilateral oophorectomy. It is rather clear that for many young women who wish to preserve their fertility, such a decision is unacceptable. Studies using LNG-IUS releasing 20 μg of LNG/day indicate that successful treatment is possible especially when such potent progestins as LNG are administered. Intrauterine route of delivery appears much more effective than oral administration. [50, 51, 52] Successful treatment of early endometrial carcinoma has been reported with a 65 μg/day progesterone-releasing IUS, followed up to 36 months, yet, results of biopsies were negative

only in 7 of 11 at 6 months and 6 of 8 at 12 months. [8] A significant reduction of the ERs and PRs expression observed during treatment with the LNG-IUS appears to be a marker for the strong antiproliferative effect of the hormone at the cellular level. Furthermore, as the treatment is continuous, compliance is not an issue.

The most common source of endogenous unopposed estrogen is chronic anovulation which can be accompanied by either continued ovarian secretion of estradiol or conversion of circulating androstenedione and testosterone to estrone and estradiol, respectively, by aromatase in the adipocytes. Chronic anovulation is a feature of PCOS and is also a condition occurring frequently in the perimenopause. In all these women, whether they have a hyperplastic condition due to exogenous or endogenous excess estrogen, direct delivery of LNG to the target cells of the endometrium using an intrauterine device will cause substantial histologic changes. The result is usually a very uniform suppression of the endometrium, regardless of the duration of treatment, the histologic picture being independent of the distance from the delivery system. [53] Intrauterine progestin delivery, particularly LNG, is therefore probably the most effective intervention in preventing endometrial proliferation because of the uniform suppression of the endometrium throughout the whole thickness of the mucosa caused by the high tissue concentrations of the locally applied hormone. With oral progestin therapy, a higher rate of residual hyperplasia, including complex and atypical hyperplasia, has been observed. [54] It has been demonstrated that the duration of the progestin administration is more important than the daily dose for prevention of endometrial hyperplasia. Again, continuous intrauterine progestin delivery seems optimal. [55]

Over the past 5 to 10 years many reports on the management of atypical endometrial hyperplasia and early cancer of the endometrium with LNG-IUS have been published. [56-63] Remissions were frequent, but also failures occurred. Some consider that at present there is no sufficient evidence because most studies were underpowered or contained a high proportion of patients lost to follow-up. [64] A meta-analysis and systematic review of the literature concludes that the available evidence suggests that treatment with oral or intrauterine progestin are of comparable effectiveness. The risk of progression during treatment is small, but longer follow-up is required. [65] As recently highlighted by Scarselli et al., who followed patients for over 15 years, LNG-IUS represents an option to treat hyperplasia and prevent endometrial carcinoma in at least 85% of patients. [66] Consistent with that study, in order to support stable regression over long periods of time, we recommend continued preventive LNG-IUS use on a life-long basis using a suitable LNG-IUS as the uterine cavity is often very small. Annual assessment of the endometrial thickness by ultrasound is probably sufficient unless vaginal bleeding occurs.

6. Concluding remarks — The future

Endometrial cancer is the fourth most common malignancy in women. Many women die each year of this potentially preventive disease. Uterine precancerous conditions and even early endometrioid cancer of the endometrium have a reasonably studied potential to respond to

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hormonal therapy. A growing body of evidence suggests that progestin therapy by means of local long-acting release of a potent progestin can promote early endometrial tumor regression and long-term remission.

Conservative management with LNG-IUS of precancerous changes and early well differentiated endometrial cancer seems particularly promising in women who wish to preserve their fertility. It is emerging as an alternative to oral progestins as higher regression and lower hysterectomy rates for the treatment of complex and atypical hyperplasia are achieved with the device. LNG-IUS should, therefore, be the first-line primary prevention treatment. [67-75] However, conservative treatment carries an inherent oncologic risk as no correct staging is possible and the risk of missing a concurrent ovarian cancer cannot be neglected. Pre-treatment evaluation should include assessment for genetic conditions predisposing to cancer, such as Lynch syndrome. It is apparent that the ideal candidates for conservative cancer treatment are young women with grade 1, early stage endometrioid endometrial cancer (T1) with no detectable myometrial invasion who are highly motivated to maintain their reproductive potential and understand and are willing to accept the risk associated with deviation from the established standard of care. [59, 76] Progestins rather than progesterone should be considered the ultimate tumor suppressors as they powerfully promote differentiation, cell cycle arrest and apoptosis, and reduce inflammation and the invasion associated with metastasis. [37] Patients in whom the treatment fails should be evaluated by immunochemistry on endometrial biopsies as treatment failure is often caused by loss of PR expression. Clinical research is currently underway focusing on maintaining PR levels or identifying novel therapeutic approaches that restore PR expression in tumors from which it has been lost. [38, 77] Failure could also occur simply due to the downward displacement of the hormone-releasing IUS causing less impact on areas away from the IUS. Proper distribution of the hormone to the deeper layers of the endometrium seems essential to achieve maximum impact.

As the lifetime risk of endometrial cancer in anovulating obese women is 15% or more, one could assume that many of these cancers could be prevented using LNG-IUS. We support such an approach together with others who believe that it could be successful provided that suitable LNG-releasing intrauterine delivery systems are used. The latter is important as the uterine cavities in women of any age are often small and even become smaller with the use of LNG-IUS. Side effects such as displacement, embedment and expulsion are not rare, leading to early discontinuation. [78] Leslie at al. hope that the following will be possible in the future: "As a profession, we should ask ourselves if we can not only treat, but prevent a substantial proportion of endometrial cancers with more liberal use of progestin-containing IUDs?" [79]

Apart from the emerging role of LNG-IUS for endometrial cancer prevention, as reviewed recently by Jóźwik et al. [80], the future might lead us to even more effective hormone-releasing IUDs. It was proposed that local delivery of other drugs such as mifepristone or ulipristal, with their strong antiprogestin activity and antiestrogenic effect at the endometrial level, may be more suitable than LNG to act as tumor suppressor. No studies with intrauterine delivery of these agents have been conducted so far. However, one example is worth mentioning which indicates the potential of these compounds: A 48-year old nulliparous woman was consulted

by one of the authors (DW) in 2007 for bleeding problems. It was known that she suffered from multiple uterine leiomyomas which tended to increase in size significantly over the past years. A pipelle biopsy revealed atypical hyperplasia. On MRI, the uterus was increased in size with several leiomyomas, the largest being of 65 mm in diameter. A frameless mifepristone-releasing IUS was inserted on 20 January 2007. The first follow-up was done one month later. At that time, the patient mentioned some spotting and a repeat biopsy showed residual focal atypical hyperplasia. Three months after insertion, breakthrough bleeding stopped completely, the diameter of the largest myoma was reduced to 33 mm and a histological specimen showed deficient endometrium without signs of atypia. All further follow-up examinations were uneventful with no abnormal bleeding. The patient was kept on this experimental mifepristone-releasing IUS for approximately 5 years. It was replaced by a LNG-IUS at the end of 2011 and, at annual check-ups, she has remained asymptomatic.

Finally, it is worth mentioning that several large epidemiological studies pointed out the potential of metformin as an anticancer drug. Metformin is an oral antidiabetic drug and is the first-line drug for the treatment of type 2 diabetes, in particular, in overweight and obese subjects with normal kidney function. It is used for the treatment of PCOS and has been investigated for other diseases where insulin resistance seems an important factor. Metformin acts by suppressing glucose production in the liver and has a vast safety track record. Preclinical and early clinical trials suggest a role for metformin in the prevention and treatment of cancer. Its potential is still unproven, but seems extremely promising. [81] Recently, a phase 2 study was designed in Australia combining LNG-IUS with oral metformin for the treatment of complex endometrial hyperplasia with atypia and grade 1 endometrial endometrioid adenocarcinoma. [82] Hopefully, this and other careful clinical studies will path a new approach to the prevention and treatment of early endometrial cancer.

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