Conservative treatment of endometrial cancer in women of reproductive age (Review)

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Received January 24, 2023; Accepted April 18, 2023

DOI: 10.3892/mco.2023.2651

Abstract. Endometrial cancer is the fifth most common female cancer worldwide and the third leading female cancer in the Western world. The marked surge in endometrial cancer incidence is alarming. The aim of the present review is to focus on endometrial cancer affecting young women of reproductive age. Surgery, namely abdominal or laparoscopic hysterectomy, with or without salpingo-oophorectomy, and sentinel lymph node detection has become the standard surgical strategy for early stage endometrioid endometrial cancer. However, premenopausal women might want to preserve their fertility, especially if they are nulliparous or have not reached their desired number of children at the time of diagnosis. Conservative, uterus-sparing treatment, based on progestin products, may be an advantageous option for patients meeting the necessary criteria. Potential candidates have to be committed to following a rigorous protocol of treatment, investigations and follow-up. The evidence in favor of this approach, although limited, is encouraging and patients who have achieved a histologically documented disease complete remission could attempt to conceive spontaneously or with the immediate use of assisted reproductive technology techniques. The risk of partial or negative response to progestin treatment or cancer recurrence is well documented, thus patients have to be aware of the possible need for interruption of conservative treatment and hysterectomy.

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Abbreviations: ART, assisted reproductive technology; EC, endometrial cancer; SERMs, selective estrogen receptor modulators; PCOS, polycystic ovarian syndrome; EIN, endometrioid intra-epithelial neoplasia; MRI, magnetic resonance imaging; LNM, lymph-node metastases; D&C, dilation and curettage; MI, myometrial invasion; TVUS, transvaginal ultrasound; LNG-IUD, levonorgestrel intrauterine device; GnRHa, gonadotropin-releasing-hormone agonists; SERDs, selective estrogen receptor degraders; AIs, aromatase inhibitors; MA, megestrole acetate; MPA, medroxyprogesterone acetate; ER, estrogen receptor; PR, progestin receptor; BMI, body mass index; ESGO, European Society of Gynaecological Oncology; CAEH, complex atypical endometrial hyperplasia; PDT, photodynamic therapy; POLE, polymerase epsilon; MMR, mismatch repair

Key words: EC, young women, early stage, conservative treatment, fertility sparing

Contents

1. Introduction

Worldwide, Endometrial Cancer (EC) is the second most common gynecological malignancy after cervical cancer (1-4). Its incidence has been steadily increasing in recent years, especially in developed countries, ranking 7th among the most lethal malignancies in Western Europe and 3rd in the USA (3,5). Its rising incidence can be partially attributed to the modern way of life, with obesity and sedentary lifestyle playing a major role. In the majority of cases, EC is driven by estrogen dominance, which is especially prevalent in obese women due to the aromatization in adipose tissue (2). Alongside its raising incidence, it seems to be affecting increasingly younger women. The majority consists of menopausal women, comprising 75% of all affected women. The other 25% involves premenopausal women, with 10% pertaining to women <45 years old (3,6) and 4-7% to women aged 20-44 years old (3,7). It must be noted that, while rare, EC can also affect adolescent women; two cases of an 11-year-old and a 13-year-old patient have been reported (7). The standard surgical treatment for endometrial cancer is total abdominal hysterectomy, bilateral salpingo-oophorectomy and staging lymphadenectomy or sentinel node identification, a de facto fertility cancellation treatment. The steadily increasing worldwide incidence of EC, combined with a constantly increasing age of childbearing in the developed countries, means that more and more young women will be diagnosed with EC in the future (8,9). The current review aims to highlight issues upon therapeutic strategies in young women diagnosed with EC, who want to preserve their fertility potential.

2. Methods

A narrative review was performed focusing on conservative treatment of endometrial cancer in young women of reproductive age. A Medline search was performed, using the terms Conservative Treatment, Endometrial Cancer/EIN, Young Women, Fertility-Sparing and the boolean operators AND and OR. Articles published from 2000 onwards were considered and the last search was performed in February 2023. Only articles published in English were considered.

3. EC risk factors

The most important risk factors for endometrial cancer are the increasing age, genetic syndromes, in particular Lynch Syndrome, also known as HNPCC (hereditary non-polyposis colon cancer) (1,5) and less so, Turner Syndrome and Cowden Syndrome (7), familiar history of EC, individual history of ovarian cancer and, particularly, breast cancer treated with Tamoxifen, a Selective Estrogen Receptor Modulator(SERM), which acts as an agonist on endometrial estrogen receptors, individual history of Polycystic Ovarian Syndrome(PCOS), unopposed and prolonged estrogenic action, obesity, type II diabetes mellitus, arterial hypertension, nulliparity, individual history of endometrial hyperplasia, individual history of radiotherapy, early menarche and late menopause and geographical distribution, with European and North American women at greater risk.

On the contrary, smoking is associated with a lower risk of endometrial cancer, especially in postmenopausal women, through a proposed anti-estrogenic mechanism (1,2,5).

4. Selection criteria for conservative treatment

A summary of the selection criteria, as outlined by several medical societies, is provided below (10,11): Presence of complex atypical hyperplasia/endometrioid intra-epithelial neoplasia (EIN) or well-differentiated (grade 1) endometrioid EC, FIGO histological stage IA without myometrial invasion (Table I) (12,13), no evidence of myometrial invasion as demonstrated by imaging examinations, preferably Magnetic Resonance Imaging (MRI), no evidence of lymph node metastases (both pelvic and para-aortic), no evidence of synchronous ovarian cancer, the patient is thoroughly informed that the oncological safety is based on retrospective or non-randomized data and, following treatment, she will have to undergo a hysterectomy, close collaboration with a fertility expert in the Gynecologic team is mandatory, as often these patients undergo immediate *in vitro* fertilization, following successful remission of EC and the patient is willing to commit to the treatment protocol and the appropriate follow-up examinations required (2,4,14)

5. Histopathology

There are two histological types of EC: type I (endometrioid carcinoma), affecting younger patients, which is mostly driven by circulating estrogen excess and has a favorable prognosis, and type II (mostly serous carcinoma), which affects more often older women and has a poorer prognosis (8).

The COG-33 study has assessed the risk of nodal involvement according to the histological grade. Grade 1 tumors confined to the inner third myometrium presented a 3% risk of lymph node metastases (LNM), while deep myometrial invasion was associated with an 11% risk. In contrast, the risk of nodal involvement increased significantly in the case of grade 3 tumors; those restricted to the inner third of the myometrium presented a 5% risk, whereas deep myometrial invasion increased the risk up to 34% (15). A more recent study has shown that the risk of LNM in grade 1 tumors without myometrial invasion may be as low as 0.5%, rising to 1.6% for higher grade tumors without any myometrial invasion (16).

Based on the above risk assessment of LNM, women with an endometrioid grade 1 EC, without any evidence of myometrial invasion, are considered suitable for conservative treatment. However, high-grade endometrioid tumors, with any evidence of myometrial invasion, are considered contraindications for conservative treatment.

6. Diagnosis

The methods of obtaining histological specimens and assessing myometrial invasion are key elements for selecting appropriate candidates for conservative treatment. Pipelle endometrial biopsy has been reported as presenting a diagnostic accuracy for EC of 91% in the general population; therefore, it can be a useful initial tool (17). However, studies show that it is inferior to dilatation and curettage (D&C) in defining

Table I. International Federation of Gynecology and Obstetrics staging for endometrial cancer.

Stage	Features
I	Tumor confined to the corpus uteri
Ia	No or <50% myometrial invasion
Ib	Invasion ≥50% of the myometrium
II	Tumor invades cervical stroma but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIa	Tumor invades serosa of the corpus uteri and/or adnexa
IIIb	Vaginal and/or parametrial involvement
IIIc1	Positive pelvic lymph nodes
IIIc2	Positive para-aortic lymph nodes with or without pelvic nodes
IV	Tumor invades bladder and/or bowel, and/or distant metastases
IVa	Tumor invasion of bladder and/or bowel mucosa
IVb	Distant metastases, including intra-abdominal and/or inguinal lymph nodes

accurately the histological grade, possibly due to the small volume of tissue obtained by the pipelle (18). Hysteroscopic diagnosis is regarded as the gold standard, having been shown to be superior to both the pipelle and D&C methods in terms of diagnostic accuracy (5,7,19,20). Direct visualization allows real-time evaluation of the endometrial cavity, with accurate endometrial sampling and more effective disease removal. Importantly, owing to the high inter-observer variations in histological grade evaluation, it is mandatory that, in case of candidates for conservative treatment, tissue samples should be assessed by two experienced pathologists.

Accurate assessment of myometrial invasion (MI) is challenging, as it can be done only using a hysterectomy specimen. However, indirect assessment of myometrial invasion can be performed using a sensitive imaging technique. Contrast-enhanced MRI provides a high diagnostic accuracy, although studies show that transvaginal ultrasound (TVUS) has the same sensitivity at a much lower cost. MRI with diffuse weight imaging is considered the method of choice, although a recent meta-analysis concluded that TVUS is not inferior to MRI for evaluating myometrial invasion, especially in the case of experienced operators (21). The 3D TVUS has been shown to be of equal performance in assessing myometrial invasion (22), although this was recently challenged in a multi-centered study, showing inferior specificity with TVUS (23). A major advantage of MRI, compared to ultrasound, is that it provides additional information regarding cervical stroma involvement, as well as the lymph node status. Thus, MRI is considered the method of radiological choice in assessing patients for enrollment in fertility sparing treatment.

The recent 2023 European guidelines stress the importance of documenting myometrial invasion with the Hysteroscopic Resectoscope, which could not only define the depth of MI but, also, remove the entire lesion endoscopically (24).

7. Pharmacological fertility-sparing treatment

i) Oral Progestins, ii) Levonorgestrel-releasing Intrauterine Device (MIRENA), iii) Gonadotropin-releasing-hormone-agonists, iv) Selective Estrogen Receptor Modulators (SERMs), v) Selective Estrogen Receptor Degraders (SERDs) (5), Aromatase inhibitors (AIs) (24), vi) Metformin (Fig. 1) (5,25-28).

8. Progestins

This is the most commonly employed conservative treatment. Although initially reported in 1961 (2), the first study confirming their effectiveness was published in 1997 (29). Their mechanism of action is via opposition of estrogen-driven endometrial growth, resulting in thinning of the endometrium and stromal decidualization. This effect is thought to be exerted through down-regulation of estrogen receptors, activation of enzymes involved in estrogen mechanism, regulation of the cell cycle by cyclin-dependent kinases and enhancement of p27 expression, causing inhibition of cyclin E-Cdk2 function and suppression of the cell cycle (7,30,31).

The two progestins commonly used are megestrol acetate (MA) and medroxyprogesterone acetate (MPA) (30). The optimal dosage and duration of the therapy are still under investigation; however, the dose most often employed is 160 mg/day for MA and 400-600 mg/day for MPA (7,13,30). However, treatment with MA has been shown to carry a higher risk of disease recurrence, highlighting the need for further investigation (30,32). Also, the optimal duration of therapy has not been established yet. According to many studies, the median duration of treatment needed for a complete histopathological response is 3 months (33). Lack of histologically documented response to progestins is considered as a failure of conservative treatment (34). In the case of a partial response, the dosage can be increased with regular follow-up at 3-months intervals. In total, a duration of 9-12 months is expected to result in complete response in women who fulfill the strict criteria, which were outlined earlier in the text (3,30).

Additionally, many hormonal receptors and other immunohistochemical markers are being investigated as predictive markers (35). The most well-established marker for predicting proportionally the efficacy of MA/MPA therapy, is the proportion of estrogen and progesterone receptors in the pathological endometrium. Their implications from disease pathogenesis

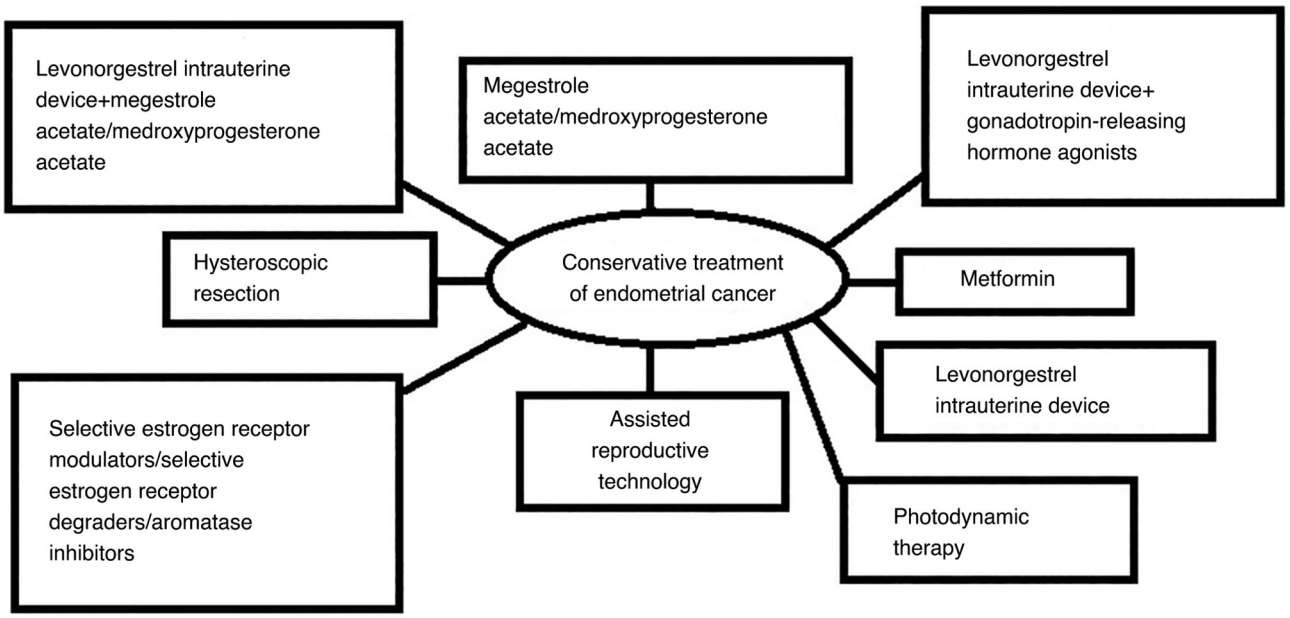

Figure 1. Conservative methods of treatment in endometrial cancer.

to treatment response have been extensively documented, with the PRB isoform of the progesterone receptor being the most studied (31,35). Other pathways involving PTEN, MMR, Dusp6 and GRP78 genes have also been studied, with the hope of providing targeted therapy options in the future (31,35-37).

Another promising perspective in the conservative treatment of EC is the addition of metformin to MA/MPA therapy. Metformin acts synergistically with progestins, inhibiting the PI3K-AKT-mTor oncogenic pathway and increasing the expression of PR receptors (13,36,38).

The reported response rate of EC to treatment with progestins is, approximately, 75%, although in earlier case-studies no strict criteria selection were used for including patients for analysis (30). However, high oral doses of progestin increase the risk of complications, most notably weight gain, reduction of libido, mood changes, leg cramps, headaches and thromboembolic events (30). As far as weight gain is concerned, pre-treatment and post-treatment BMI>25 kg/m^2 is significantly associated with a higher rate of disease recurrence, due to peripheral aromatization of adipose tissue, underlining the importance of maintaining a normal BMI during treatment with progestins (7).

9. Levonorgestrel-releasing intrauterine device (LNG-IUD) (MIRENA)

In the past few years, a new type of progestin therapy, free of the above side effects, has been proposed. The so-called MIRENA is an endometrial device that releases 25 μg/day of levonogestrel at a continuous rate inside the uterine cavity, thus avoiding the adverse effects of oral administration (37). Furthermore, higher progestin concentrations can be achieved locally, increasing their efficacy. The results are very promising, especially for cases of atypical endometrial hyperplasia, with regression rates approaching 90%. Contrary to oral progestin therapy, LNG-IUD should be used with caution in women with an enlarged uterus, because there is a risk of misplacement in the endometrial cavity and treatment failure (39).

10. LNG-IUD and oral progestins

Several studies have suggested that the local usage of LNG-IUD, combined with a systemic high-dose of progestin, might be a more effective type of treatment for EC. Oral progestins lead to high plasma concentrations but low local concentrations in the endometrium, especially in obese women. Conversely, LNG-IUD releases highly effective progestins into the endometrium, with a 30-times higher median concentration than in the plasma. According to the latest ESGO guidelines, the combination of LNG-IUD and oral progestin therapy is the most effective treatment, providing a low recurrence rate and a satisfactory pregnancy rate (13). However, the efficacy of this combination for patients with EC has not been well investigated. It remains unknown the reason why the combined MA with local LNG-IUD did not achieve better treatment efficacy than MA alone in some studies. Oral MA may achieve adequate concentration of progestins for EC treatment without the additional of local levonogestrel. A recent Korean study showed that the combined LNG-IUD with oral MPA (500 mg daily) is more effective than the use of LNG-IUD alone (9). Also, a gynecologic oncology group study reported that low-dose MPA (200 mg/day) was more effective than high-dose treatment (1 g/day) (40). More research is needed to elucidate what is the ideal monotherapy or combined progestin treatment.

11. LNG-IUD and GnRHa

Another therapeutic option is the combination of LNG-IUD and GnRHa (gonadotropin-releasing hormone agonists) (16). A meta-analysis, combining data from six studies, showed a satisfactory pregnancy and low recurrence rate (9,14). After one year of LNG-IUD combined with GnRH analogs, up to

57% of EC and 95% of EIN achieved a complete response, with a pregnancy rate of 85% and a recurrence rate of 20% (41).

12. SERMs/SERDs/AIs

There are several anti-estrogenic drugs, which could be potential therapeutic candidates for the conservative treatment of EC. These include SERMs (tissue-selective agonist or antagonist action on ERs) with raloxifene and arzoxifene blocking estrogen receptors, excluding Tamoxifen, which has both stimulatory and blocking effects, SERDs (mainly Fulvestrant, which down-regulates ERs) and aromatase inhibitors, such as letrozole (decrease of systemic exposure to estrogens by inhibition of the peripheral conversion of androgens to estrogens).

It has been postulated that any of the above could be used as a primary treatment for obese EC patients or as a second-line treatment, after initial failure of progestins alone (7).

13. Metformin

Metformin has been shown to inhibit proliferation and migration of endometrial cancer cells *in vitro*. Additionally, it has been reported to upregulate progesterone receptors, making endometrial cancer cells more sensitive to progesterone interventions (42). The theory of metformin administration in endometrial cancer conservative treatment has been developed as a result of the interaction between glucose metabolism and endometrial cancer development and progression. Apart from the immediate effect of metformin on endometrial cancer cells described above, metformin downregulates circulating insulin-a result of insulin resistance, which in turn acts as a growth factor for endometrial cancer cells (28). Furthermore, except for the direct effect of metformin on endometrial cancer, metformin also helps with reversing the consequences of metabolic syndrome Notably, obese women with metabolic syndrome are considered of poorer prognosis compared to women with normal BMI (43). Furthermore, in the case of polycystic ovary syndrome (PCOS), reversal of insulin resistance may lead to normal ovarian function, minimizing the long estrogenic effect of anovulation to the endometrium. Recently, it was shown that PCOS acts as a negative prognosticator for conservative treatment in case of Complex Atypical Endometrial Hyperplasia (CAEH) or well differentiated endometrial cancer (43). In contrast, metformin has been shown to accelerate the time of complete remission, especially in women with increased BMI (27). A recent meta-analysis reported that metformin, combined with progestins, was associated with lower relapse rates, without significant impact on oncological and reproductive outcomes (26). There are also several ongoing or forthcoming trials for the use of metformin in EC women. In 2013, NCT01968317 began comparing metformin plus MA with MA alone, as an option for fertility-sparing treatment in patients with EIN and well-differentiated EC. Metformin is cheap and has an excellent safety profile, so it appears to be an obvious choice for prospective randomized studies (44).

14. Other fertility-sparing treatments

i) Hysteroscopic Resection, ii) Photodynamic Therapy, iii) Assisted Reproductive Technology (Fig. 1) (7,14,33).

15. Hysteroscopic resection

Hysteroscopic resection is the gold standard for the diagnosis and treatment of intracavitary pathology of the uterus. Hysteroscopic resection can be attempted for localized endometrial hyperplastic/malignant lesions. This initial approach in hysteroscopic resection of endometrial cancer has been described as a 3-step-process: a) resection of the lesion, b) resection of the adjacent endometrium and c) resection of the underlying myometrium (45). The resection was mandatorily followed by treatment with progestins or LNG-IUD placement (4,16). A more recent approach has added multiple hysteroscopically-guided endometrial biopsies to increase further the sensitivity of the method (46). Several small studies have been published with supportive results. The most robust study in terms of sample size (140 cases of CAEH and 40 cases of endometrial cancer) showed that this type of treatment yields better overall results in a shorter time frame, provided that the initial tumor size is <2 cm, and the patient's BMI is <25 kg/m^2 (47). The produced evidence has been incorporated in the 2021 ESGO guidelines (13). The excellent regression rates achieved after hysteroscopic resection are explained by the hysteroscopic cytoreductive effect on the primary tumor, which may increase the effectiveness of the progestin therapy.

The latest 2022 ESGO guidelines highlight the utmost importance of hysteroscopic biopsy for diagnosis and resectoscopic resection in order to maximize progestin therapy (41).

16. Photodynamic therapy

This is an innovative type of EC treatment that has also been described as a therapeutic option for malignancies of other sites, namely vagina, cervix, bladder and esophagus. Besides the current clinical indications, PDT constitutes a dynamic area of research with huge potential to be considered as a valid treatment option for a wide range of diseases. It works by exposing the affected area to a specific wavelength of light, which is selectively toxic to the cancer cells. PDT has been tried both as a primary and as an adjuvant therapy in cases of disease regression after fertility preservation. The results were encouraging for both disease regression and fertility preservation. PDT presents significant advantages; it is a local, highly selective, and minimally invasive therapy (41). The single reported side effect was facial angioedema, presenting at a rate of 25%. Further clinical trials are needed for PDT to be established as a safe conservative treatment for EC (33).

17. Assisted reproductive technology (ART)

When hysterectomy with bilateral salpingo-oophorectomy is considered as the therapeutic option, ART can be applied before definitive treatment for the patient to conceive through surrogacy (48). There are many options, including freezing of oocytes, embryos or even ovarian tissue. Except for the need for surrogacy, the main advantages are the quality of the cryopreserved tissues upon using the innovative method of vitrification and that the procedure can be very expeditious, by selecting ovarian tissue by laparoscopy, as one-day hospital procedure, or with random-start protocols for ovarian stimulation (49). In these cases, letrozole is the preferred agent, as

it does not seem to stimulate the endometrium. Alternatively, a random-start protocol consists of the administration of gonadotropins any day of the menstrual cycle (late follicular, peri-ovulatory or even the luteal phase). The main advantages of this protocol are shorter time to complete the fertility preservation treatment and, also, it can be applied in any patient, even for those who have intrauterine devices. Leaving the IUD in place has the added benefit of mitigating the endometrial growth driven by estradiol, which happens during ovarian stimulation. Another ovarian stimulation protocol is called 'duo-stimulation', consisting of a double egg retrieval procedure in a 28-day time frame, with the initiation of a second ovarian stimulation cycle 4 days after the first egg collection (50). By adopting any of these methods, delays of definite surgical treatment can be avoided (7).

18. Fertility outcomes

The strongest motive towards a conservative approach is the patient's childbearing desire. The rate of women who have successfully conceived and given birth after treatment cannot be accurately estimated, fluctuating between 25 and 100%, because not all the patients who have undergone conservative treatment were planning to conceive in the first place (51). Despite the fact that women who choose conservative treatment are determined to achieve a future pregnancy, there might be several medical or social reasons for the apparent divide between what is observed in clinical trials and what happens in real life. Certainly, from this point of view, the best candidate is a patient in a stable relationship, ready to conceive after successful regression of the disease. There are several factors that have been positively associated with a successful pregnancy, including a normal BMI during conception and gestation a shorter time interval to complete remission, whereas a thinner endometrium and disease relapse before conception are considered to have a negative effect (52). After a histologically documented disease remission, women can begin their efforts to conceive with safety. This can be achieved even spontaneously or with the use of assisted reproductive technology (ART). Most often, young women with EC already have a documented history of infertility, because of overlap in the pathogenic mechanisms, mainly PCOS and anovulation. Despite broad consensus regarding the main oncological criteria for candidate selection, it has not been extensively investigated as to how each candidate's reproductive prognosis should be evaluated and used to support decision-making. Another important issue is the duration of conservative treatment in women who are not ready to conceive following complete regression. It is generally accepted that the patient may carry the LNG-IUD for longer periods, as long as she undergoes an endometrial biopsy every six months (13,53). Therefore, the guidance of an experienced medical professional specializing in infertility is always advised. Generally, immediate ART is advised to decrease the risk of recurrence, staying without treatment for a long time. However, an eventual pregnancy is not a risk factor in itself for disease recurrence (19,31,36,51,54).

19. Follow-up

After a successful pregnancy, women undergoing conservative treatment should be advised to proceed to definite treatment, which is a hysterectomy and bilateral oophorectomy. However, women who want to achieve a second pregnancy can be followed up with a strict protocol of 3-6 month examinations, including hysteroscopic biopsies (25). If a patient wants to delay a second pregnancy, maintenance therapy using low-dose cyclic progestin, or an LNG-IUD can be suggested.

20. Progress in basic research

Endometrial biopsy and histopathological examination can be unreliable in predicting risk of disease recurrence owing to errors in correct histological sampling and significant variability of histological interpretation. New biomarkers for EC risk classification are being investigated. The Cancer Genome Atlas identified four molecular subtypes of endometrial cancer, which are: POLE ultramutated (POLEmut), MMR deficient (MMRd), nonspecific molecular profile and p53 abnormal (p53abn) endometrial cancer, the POLE variant being the least aggressive molecular type. The molecular classification is likely to be used in the future and incorporated even in the management of young patients wishing to preserve their fertility (32,36,55).

21. Pushing the boundaries

Fertility-sparing treatment in EC has been investigated without a defined consensus in recent years. The difficulty of defining its boundaries may be related to many factors that influence its success. The most important issues are the assessment of the tumor's clinicopathological profile (histological type and grade, myometrial invasion, presence of lymph-vascular space invasion), choosing the optimal type, duration, and dose of medical treatment, and the appropriate follow-up (56).

Despite the strong desire of fertility preservation with certain patients not in the above ideal profile, it has to be stressed that International Societies Guidelines have to be implemented. There are certain cases which seem to respond favorably, and with no extra oncological risk, to treatment. For example, Endometrioid Tumors of Histological Grade 2 and those with early myometrial invasion. It is advisable to discuss all cases in a Multidisciplinary Tumor Board Meeting and to enroll such patients to appropriate trials, having signed a detailed informed consent form (57,58).

22. Conclusion

Endometrial cancer can affect a small, albeit increasing, proportion of nulliparous young women who want to achieve childbearing. So far, the mounting scientific evidence shows that, in the case of a very early Endometrioid, Grade 1 Endometrial Cancer, this is possible and oncologically safe.

Conservative treatment for EC is not suitable for all women, but it can be offered on an individual basis, following a meticulous medical examination, imaging, hysteroscopic evaluation and expert histological diagnosis. Such patients, willing to cooperate with a strict therapeutic protocol, have a high chance of achieving a successful pregnancy. Preferably, immediate ART technique is used, to maximize the chances of conceiving and not leaving the patient without treatment for long periods.

With the available evidence, women who do not want to conceive immediately after successful pharmaceutical disease regression, or after a first pregnancy, can wear the LNG-IUD and undergo endometrial biopsies on a regular basis. In this case, it is advisable to undergo ovarian tissue preservation, preferably egg freezing.

All individual cases have to be discussed in a Multidisciplinary Tumor Board and all patients have to be thoroughly informed and sign a consent form for the treatment and follow-up. It has to be clear in their minds that the treatment does not cure the cancer, but it suppresses it enough to achieve a pregnancy. It has to be clearly said and written in their consent form that, after a successful pregnancy, a hysterectomy has to take place.

Developments of new therapeutic strategies are very exciting and, especially, metformin appears to be a pivotal agent to achieve disease regression. Of course, the latter refers to the majority of these patients, with a typical metabolic profile of obesity, PCOS and anovulation.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

TP, MZB, AM and TV conceived the concept and wrote the manuscript. GM and GV critically revised the manuscript for intellectual content. TP organized and revised the final version of the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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