Safe Fertility-Preserving Management in Endometrial Cancer: Is It Feasible? Review of the Literature

Márcia Mendonça Carneiro, MD, PhD,[1,4] Rívia Mara Lamaita, MD, PhD,[2]
Márcia Cristina França Ferreira, MD, PhD,[1,3] and Agnaldo Lopes Silva-Filho, MD, PhD[1]

Abstract

Almost 5% of women with endometrial cancer are under the age of 40, and often have well-differentiated endometrioid estrogen-dependent tumors. Frequently, these women have a strong desire to preserve fertility. Strategies to avoid or reduce the reproductive damage caused by surgery, cytotoxic agents, and radiation are needed. This review addresses options available for safe fertility preservation in endometrial cancer.

Clinical treatment with progestin agents may be prescribed after careful evaluation and extensive counseling. Strict criteria should be employed to select suitable patients, using imaging methods and endometrial sampling, once it has been established that standard surgical staging will not be performed. Conservative fertility-sparing treatment should only be offered to patients with a grade 1 well-differentiated tumor, absence of lymph vascular space invasion, no evidence of myometrial invasion, metastatic disease, or suspicious adnexal masses, and strong and diffuse expression of progesterone receptors on immunohistochemistry staining of the endometrial specimen. The presence of co-existing ovarian metastatic of synchronous cancer should be investigated and excluded before the decision to preserve the ovaries.

In addition to these conservative therapeutic options, the use of assisted reproductive technology (ART) has made it possible for women with endometrial cancer to give birth to a child without compromising their prognosis. Gamete, embryo, or ovarian tissue cryopreservation techniques can also be employed, although some of these are still considered experimental.

Fertility preservation is infrequently applied in the cancer population, and there are scarce good quality studies in the literature, which makes careful staging, thorough counseling, and close follow-up of the patients imperative so as not to jeopardize cancer cure. (J GYNECOL SURG 28:399)

Introduction

CURE REMAINS THE MOST IMPORTANT GOAL of cancer treatment, and definite therapies available are based on surgery, cytotoxic medications, and/or radiation. These procedures, however, result in partial or total loss of fertility. Cancer incidence continues to increase worldwide, largely due to aging and growth of the world population alongside an increasing adoption of cancer-causing behaviors, particularly smoking, in economically developing countries.[1] During the last two decades, however, cancer survival has improved, resulting in an increased focus on improving quality-of-life issues for women who survive cancer, and this includes fertility care.[2–4]

As gynecologic malignancies often affect young women who are still in their reproductive years and because women are conceiving at a more advanced age, the incidence of cancer in those who still want to become pregnant is increasing significantly. Rates of permanent infertility and compromised fertility after cancer treatment vary and depend on many factors. The effects of chemotherapy and radiation therapy depend on the drug or size/location of the radiation field, dose, dose intensity, method of administration, disease, age, sex, and pretreatment fertility of the patient. A more conservative management, which preserves fertility, is considered a safe option for those who have not completed their child bearing.[2,4] New methods for women, such as in vitro follicle maturation and techniques for tissue

[1]Department of Obstetrics and Gynecology, Universidade Federal de Minas Gerais, Brazil.
[2]Pró-Criar Clinic of Assisted Reproduction, MaterDei Hospital, Belo Horizonte, Minas Gerais, Brazil.
[3]Universidade Federal de Ouro Preto (UFOP), Ouro Preto, Minas Gerais, Brazil.
[4]CAPES Foundation, Ministry of Education of Brazil. Postdoctoral Scholarship BEX3965/11-2.

transplantation, are on the horizon.[5] The FIGO Committee for the Ethical Aspects of Human Reproduction and Women's Health states that the treatment of the cancer is the primary medical goal, and risks of delaying treatment in order to induce ovarian stimulation and retrieval or ovarian removal or transplant must be carefully considered and should not have a significant impact on treatment.[6]

Endometrial carcinoma is the most common female pelvic malignancy in developed countries and accounted for approximately 43,470 new cases and 7,950 deaths in 2010.[1] Although it is primarily a disease of the postmenopausal female, 25% are premenopausal and 3–5% are under the age of 40.[1,7] This younger group with endometrial cancer tends to have a history of ovary dysfunctions, anovulation, infertility, and obesity. Frequently, these women are nulligravid and have a strong desire to preserve fertility. The carcinoma of the endometrium in such patients is usually an estrogen-dependent well-differentiated endometrioid carcinoma. These malignancies do not tend to invade the myometrium and are associated with a good prognosis.[7,8] Selected patients with endometrial cancer may be candidates for a conservative approach, preserving their fertility potential.[9]

We performed a review of the relevant articles without language restriction based on a PUBMED search of the keywords: "fertility preservation," "endometrial cancer," "surgical treatment," "pregnancy," "chemotherapy," and "radiation." We reviewed the available literature about safe fertility-preserving management in endometrial malignancies, focusing on the selection criteria of the patients, treatment options, and follow-up. We aimed to answer the following questions. How should reproductive-age women with endometrial cancer be evaluated? Is fertility preservation in endometrial cancer safe? What is the effect of pregnancy on endometrial cancer? What are the options available?

How Should Reproductive-Age Women with Endometrial Cancer Be Evaluated?

The standard treatment for endometrioid carcinoma includes staging laparotomy, total abdominal hysterectomy, and bilateral salpingo-oophorectomy with pelvic washing and lymph node sampling when appropriate. The 5-year survival rate after this approach is approximately 94%.[8,10] However, this therapeutic option may be too radical for women who desire to preserve fertility. Currently, fertility-preserving options in endometrial cancer are limited to hormonal methods.[11–13] Patients desiring to proceed with conservative hormonal management should be extensively counseled regarding potential risks, as no scientifically proven optimal progestin regimen exists.[14] Response to treatment is variable and depends on tumor receptor status, ranging from 26% to 89% in estrogen and progesterone positive tumors. However, it can be as low as 8–17% when these receptors are absent.[7,15–17]

The conservative treatment of endometrial carcinoma may be recommended when a patient desires to preserve fertility, the tumor is endometrioid, and its clinical stage is IA FIGO and histological FIGO grade I. It is important to emphasize that this is not standard procedure and should be considered only if the patient insists. Careful and thorough counseling is mandatory in these circumstances.[14]

Adequate clinical staging of endometrial cancer remains a challenge, thus surgical staging is the gold standard. Prognosis depends on histological grade, depth of myometrial invasion, cervical involvement, vascular space involvement, pelvic and aortic lymph node metastases, adnexal metastases, and positive peritoneal cytology. No optimal method of evaluation prior to conservative management has been identified so far, hence multiple noninvasive or minimally invasive modalities are employed to attempt to "clinically stage" a patient.[18,19]

Routine blood and urine studies should be performed and serum levels of cancer antigen 125 (CA-125) should be obtained, once elevated levels suggest advanced disease. Endometrial biopsy is mandatory in the initial evaluation because the histological grade of the tumor is one of the most important prognostic factors.[18] To improve the accuracy of clinical staging, different radiological modalities have been used. Transvaginal ultrasound (TVUS), computed tomography (CT), and magnetic resonance imaging (MRI) have been tested, and studies have revealed no significant difference in their performance. However, contrast-enhanced MRI performed significantly better in the evaluation of the myometrial invasion than non-enhanced MRI, CT, or TVUS ($p < 0.02$).[19,20] When evaluation is inconclusive, laparoscopic exploration with peritoneal cytology, pelvic lymph nodes sampling, and adnexal evaluation should be considered before conservative treatment.[9,15]

Is Fertility Preservation in Endometrial Cancer Safe?

Endometrial carcinoma in patients under the age of 45 is an unusual condition and appears to show a more favorable pattern than in older patients. Premenopausal women appear to have a higher rate of low-grade tumors and lower stage of disease, resulting in a favorable 5-year disease-specific survival rate of 93%, compared with 86% for older patients.[15,21,22] However, endometrial carcinoma diagnosed at a younger age increases the additional risk of cancers associated with the Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, as well as synchronous or metachronous ovarian cancers occurring outside the setting of Lynch/HNPCC.[23,24] In these women, clinical stage I endometrial carcinoma with metastasis to the ovary is rare, occurring in 5% of cases. The incidence of any stage endometrial carcinoma with a synchronous ovarian malignancy, however, could range as high as 10–29.4%.[15,25]

Navarria et al. studied 1,365 women with endometrial cancer and found no significant difference regarding tumor characteristics and survival between young and older patients, except stage of disease (more stage II in the younger group) and rate of synchronous ovarian malignancy (14% in the younger group).[25]

Another study reported a significantly higher rate of ovarian involvement (25%) and recommended caution when considering ovarian preservation in young endometrial cancer patients with early-stage disease.[26] Richter et al. evaluated 251 patients with endometrial cancer (75.3% stage I) aging 45 or younger. Eleven patients (4.4%) had a synchronous serous ovarian malignancy, and those who underwent a bilateral salpingo-oophorectomy had a significantly longer disease-free survival but no improvement in overall survival.[24]

Ovarian preservation in young patients does not seem to impact adversely the recurrence of early-stage endometrial cancer either.[27] One study with 402 young women with endometrial cancer who underwent a hysterectomy with

ovarian preservation concluded that, in the absence of risk factors, a conservative approach to surgical staging is feasible, safe, and not associated with an increase in cancer-related mortality.[28] Although endometrial carcinoma is believed to be a hormone-dependent tumor, there is no direct evidence that preserved ovaries would increase the recurrence rate.[15,27] Ovarian metastasis and synchronous primary ovarian cancer in patients with stage I endometrial carcinoma seem to be correlated to histological type, depth of myometrial invasion, cervical invasion (including mucosa or/and stroma), uterine serosa extension, fallopian tube involvement, retroperitoneal lymph node metastasis, positive peritoneal cytology, and CA-125 level.[29] Thus ovarian preservation at the time of operation in younger women with stage I endometrial cancer is worth consideration only if ovarian metastasis or synchronous ovarian primary cancer are excluded.[29] Indeed, the possibility of occult ovarian metastasis inspires great caution, especially for patients with high risk factors.[26,28,29]

What is the Effect of Pregnancy on Endometrial Cancer?

It is very important to emphasize the necessity of discussing the risks of conservative treatment with the patient. Although the degree of histological differentiation is a sensitive indicator of tumor spread, 2.8% of all grade 1 lesions have pelvic node involvement and 1.7% paraaortic node involvement. Moreover, 10% of grade 1 tumors have deep muscle invasion, 6% of clinical stage I and occult stage II patients have spread of tumor to the adnexa, and 19% of patients have coexisting ovarian neoplasm.[21]

Various doses of different progestational agents have been used in an effort to preserve fertility in patients with clinical stage I endometrial carcinoma. Oral medroxyprogesterone acetate at a dose of 100–800 mg/day, megestrol acetate at a dose of 40–160 mg/day, and a combination of tamoxifen and a progestin have been used with similar results.[11,21,30–32] The follow-up of these patients under conservative treatment in the first year included serial TVUS, endometrial biopsy, and CA-125. Periodic endometrial samplings should be performed every 1 to 6 months.[33]

A systematic review of 16 non-comparative retrospective studies tried to determine the optimum follow-up of women treated with potentially curative treatment for endometrial cancer. Routine testing seems to be of limited benefit for patients at low risk of disease, since most recurrences occur in high-risk patients within 3 years and involve symptoms.[33,34]

Time requested for response to conservative treatment and its duration are not established in the literature. In available studies, the minimal time to response was 3.6 months and the treatment was maintained for 5.4 months.[11] Although there is currently no consensus as to which progestational agent to use, nor the dose and length of treatment, it appears that 62–75% of women with clinical stage I and well-differentiated adenocarcinoma respond well to progestational treatment within 3–9 months and the majority will have a long-term response.[16,35,36] Given accurate pretreatment assessment, progestin therapy is a feasible option to preserve fertility for young women with well-differentiated endometrial carcinoma or severe atypical hyperplasia of the endometrium.[13,16,17] The absence of progesterone receptors,

however, can jeopardize the success of progestin treatment.[37] Eskander et al.[14] recommend that candidates for hormonal treatment should fulfill the following criteria: (1) grade 1 well-differentiated tumor; (2) absence of lymph vascular space invasion (LVSI) on adequate curettage specimen; (3) no evidence of myometrial invasion on MRI; (4) no evidence of metastatic disease on CT imaging; (5) no evidence of a suspicious adnexal mass on CT or TVUS; and (6) strong and diffuse immunohistochemical expression of progesterone receptors on endometrial biopsy or curettage specimen.

In a recent review, the overall response rate, evaluated by endometrial biopsy every 3 months, to either medroxyprogesterone acetate or megestrol acetate was 73% in a median time of 4 months (range 1–15 months).[22] The relapse rate was 36% in a median follow-up time of 22 months (range 6–73 months). Overall, 40% of patients who responded successfully conceived; half of them using assisted reproductive technology (ART) to achieve an immediate pregnancy.

Many pregnancies after conservative management of endometrial carcinoma have been reported, some after ART.[13,38–43] Combining conservative treatment with ART may result in healthy infants without an adverse effect on oncologic prognosis.[41–43]

What Are the Available Strategies of Fertility Preservation?

For patients planning to have chemotherapy, radiotherapy, or to undergo bilateral oophorectomy, the loss of ovarian function will result in premature menopause and loss of fertility. Potential strategies for such patients include embryo or oocyte cryopreservation.[9,14] However, embryo cryopreservation is inappropriate for children and unmarried women because it involves a male partner, unless sperm donation is acceptable.[5] Embryo cryopreservation also requires superovulation, which is time consuming and not without side effects. Cancer patients respond to gonadotropins, but stimulation lasts longer and a higher total dose is required. No significant differences in the number of oocytes retrieved, matured oocytes, and the fertilization rate were observed.[44]

There are strategies to keep estrogen levels low during controlled ovarian stimulation so that estrogen-dependent cancer patients are safe and cancer recurrence is not increased.[45] Studies in breast cancer patients showed that the use of aromatase inhibitors combined with a gonadotropin-releasing hormone agonist (GNRHa) to trigger ovulation instead of human chorionic gonadotropin (hCG) may reduce estrogen exposure and the incidence of ovarian hyperstimulation syndrome. GnRHa ovulation trigger resulted in a higher number and percentage of mature oocytes and a higher number of cryopreserved embryos or oocytes compared with hCG cycles.[46] Recent evidence also indicates that there are multiple major follicle recruitment waves during the menstrual cycle, and hence the concept of a narrow window of opportunity for follicle recruitment may not be accurate. In the fertility-preservation setting, the current availability of GnRH antagonists combined with multiple recruitment waves allows the beginning of random-start controlled ovarian hyperstimulation (COH) in the late follicular or luteal phase of the menstrual cycle for embryo

cryopreservation in patients with cancer. Available data regarding late-follicular or luteal-start COH and emergency fertility preservation is still limited.[47]

The American Society for Reproductive Medicine defines oocyte cryopreservation as experimental, and states that women with cancer or other illnesses requiring immediate treatments that seriously threaten their future fertility who are considering oocyte cryopreservation should be extensively counseled. However, they may have no viable options and therefore be appropriate candidates for such treatment despite its "experimental status." Others, however, believe that preservation of unfertilized oocytes now represents an acceptable and often viable alternative, particularly for single women, and that it should be offered as a routine technique for female patients before chemo and/or radiotherapy.[5,48,49] The safety of the technique has be assessed by looking at 936 babies born from frozen oocytes from multiple centers around the world with no apparent increase in the rate of congenital anomalies.[49] Oocyte vitrification appears to be an efficient method to preserve oocytes, in terms of oocyte survival, fertilization, embryo development, and pregnancy rates, but more large controlled clinical trials are needed to corroborate this conclusion.[50]

Ovarian tissue cryopreservation offers the possibility to restore fertility by autotransplantation or in vitro culture and oocyte maturation, and may hopefully become a good choice for these patients.[51] Ovarian tissue cryopreservation has the advantages of allowing storage of a large number of gametes and be rapidly performed, at any period of the cycle, without delaying oncological treatment.[52] However, several considerations involve the creation of a bank of frozen ovarian tissue, and although several protocols of slow freezing and fast thawing showed exciting results, the real consequences of cryopreservation and the ideal protocol remain uncertain.[53]

Technical difficulties and the complex human folliculogenesis process will probably delay the development of in vitro culture systems to support human primordial follicular growth until the ovulatory stage.[54] Live offspring resulting from primordial follicles entirely developed in vitro has been reported only in mice.[55,56]

After transplantation, follicular development and restoration of hormone secretion have been observed in animal and human studies.[57] Normal young animals have been obtained in mice, rats, rabbits, and sheep.[58,59] In humans, since the first live birth after autotransplantation of cryopreserved ovarian tissue reported in 2004,[60] orthotopic reimplantation has led to the birth of 13 healthy babies, and one pregnancy after IVF has also been reported.[61] Studies based on animal models can be suitable to test new procedures, like freezing and thawing, in the search for a standard protocol of human ovary cryopreservation.[62]

Ovarian tissue cryopreservation can only be recommended as an experimental protocol, although some consider it a feasible option to preserve ovarian function and possibly fertility in young women at risk of developing premature ovarian failure.[63] More research is needed in order to enhance revascularization, reducing the follicular loss that takes place after ovarian tissue transplantation and grafting. These technologies remain investigational, and the success rate in humans is limited.[64] A study with human ovarian tissue xenografts in severe combined immunodeficient mice treated with sphingosine-1-phosphate concluded that it promoted neoangiogenesis in ovarian transplants and reduced ischemic reperfusion injury. Sphingosine-1-phosphate holds great promise to clinically enhance survival and longevity of human autologous ovarian transplants.[65]

Noninvasive techniques have attempted to minimize the gonadotoxic effect of chemotherapy by using GnRHa or oral contraceptives (OC)[66,67] to stop the maturation of the dividing oocyte, producing its involution and avoiding the noxious effect of chemotherapy on the dividing cell.[68] Studies have shown a 11.1% incidence of premature ovarian failure in patients who received GnRHa compared with 55.5% incidence in the controls. Others argue that there is an absence of conclusive evidence for the safety and efficacy of GnRHa treatment in protecting against chemotherapy-induced gonadal injury.[69,70] The proposed mechanisms of action include reduction of the number of primordial follicles entering the differentiation stage, diminished ovarian perfusion and delivery of chemotherapy to the ovaries, and a possible direct effect with upregulation of an intragonadal antiapoptotic molecule.[71]

Limited evidence is available on the fertility-preserving effect of OC. Two studies have shown lower premature ovarian failure rates in OC-treated patients: 13.2% compared with 29.8% in the controls.[66]

Final Considerations

The American Society of Clinical Oncology highlights that the fertility preservation literature reveals a paucity of large and/or randomized studies.[2] Fertility preservation methods are still relatively infrequently applied in the cancer population, limiting greater knowledge on success and effects of different interventions.

Current recommendations for conservative management are based on the overall favorable prognosis of grade 1 minimally invasive tumors, supported by a few case series and case reports, but no prospective data. Selected patients with endometrial and ovarian cancer may be candidates for safe fertility-preserving management. Careful staging and follow-up of the patients is essential to achieve success. Large multicenter trials are needed to better define selection criteria for conservative treatment, endocrine regimen of choice, optimal dosing, duration, and follow-up protocols.

Disclosure Statement

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Address correspondence to:
Márcia Mendonça Carneiro, MD, PhD
Rua Antonio Torres, 186
31030130- Belo Horizonte
Minas Gerais
Brazil

E-mail: marciamc.ufmg@gmail.com