Annals of Clinical Case Reports

Case Report
Published: 07 Oct, 2017

Levonorgestrel Intrauterine Device and Preservation of Fertility in Endometrial Cancer Grade I: Case Report and Literature Review

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Abstract

Endometrial cancer is the most frequent gynecologic cancer. Although it mainly occurs in postmenopausal women, it can hit younger patients as well. Hysterectomy is considered the standard treatment and it could represent a problem for those young women who desire to preserve fertility. A conservative management can be offered to these patients when the tumor is well differentiated and advanced stage is excluded. Several studies are available in literature about fertility-sparing treatment in young women. Progestin treatment, seem to be the most validated conservative management. We report the case of a 43 years old patient, nulliparous, diagnosed by directed biopsy guided by hysteroscopy of grade (G)1 endometrial cancer stage IA. After the conservative treatment levonorgestrel-releasing intrauterine device (LNG-IUD) (Mirena®, Bayer HealthCare Pharmaceuticals Inc.; 52 mg), the patient entered in complete remission. She conceived by *In vitro* Fertilization (IVF) treatment and delivered at 31 weeks multiple gestation by cesarean section for obstetric indication. After evaluation the case, total laparoscopic hysterectomy with bilateral salpingectomy was performed five months after delivery.

Keywords: Endometrial cancer; Fertility-sparing therapy; Progestin; Levonorgestrel-releasing intrauterine device; Reproduction; Outcomes

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Received Date: *12 Jun 2017*
Accepted Date: *15 Aug 2017*
Published Date: *07 Oct 2017*

Citation:
Antonijuan JR, Escribano G, Domínguez AMA, Borrego RS, Fabregas JP. Levonorgestrel Intrauterine Device and Preservation of Fertility in Endometrial Cancer Grade I: Case Report and Literature Review. Ann Clin Case Rep. 2017; 2: 1440.

ISSN: 2474-1655

Case Presentation

We present a case of a nulliparous patient of 43-year-old with a 12 months history of abnormal bleedings was referred on July 2013. Menarche was at age 12 and menses were irregular. The patient didn't suffer dysmenorrhea, nor other gynecologic disease.

Her body mass index was 30, she was not affected by diabetes mellitus, and her family history was negative for ovarian, uterine and colonic cancer.

After several months of irregular bleeding, a transvaginal ultrasound was carried out and showed a normal-sized, anteverted uterus with a thickened endometrium and increased vascularity within the endometrium. Ambulatory endometrial biopsy obtained with Cornier'spipelle showed endometrioid adenocarcinoma grade I. The immunohistochemical study revealed positivity for estrogen (85%) and progesterone (60%) receptors. Hysteroscopy (Betocchi® hysteroscope 5 mm, *Karl Storz*) revealed a friable and sessile mass inside the uterine cavity with atypical vascularization. Isthmus and cervix were unaffected. Magnetic resonance imaging (MRI) discarded myometrial infiltration. Lymph nodes were not involved by MRI. The patient desired future fertility and conservative management of her disease, and therefore underwent levonorgestrel-releasing IUD placement. Patients with endometrium-confined, well-differentiated, endometrioid adenocarcinoma are the proper candidates for this treatment [1]. Endometrial sampling obtained by betocchi hysteroscope in out patient basis, using semirigid grippers three months following IUD-LNG placement, showed complete regression of the adenocarcinoma. The patient has subsequently undergone endometrial sampling, using Betocchi hysteroscope (5 mm) and semirigid grippers, every three months. All specimens have been negative. Two follow-up MRI scans have been performed with no other evidence of intrauterine or metastatic disease. The patient remained without evidence of disease 10 months after initial IUD-LNG placement.

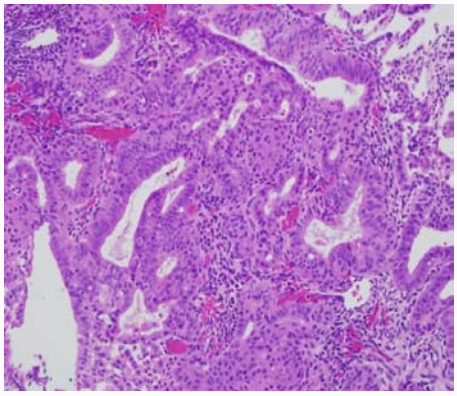

Figure 1: Well-differentiated endometrial adenocarcinoma without lymphatic vascular invasion. The arrow indicates the most representative area of endometrial cancer.

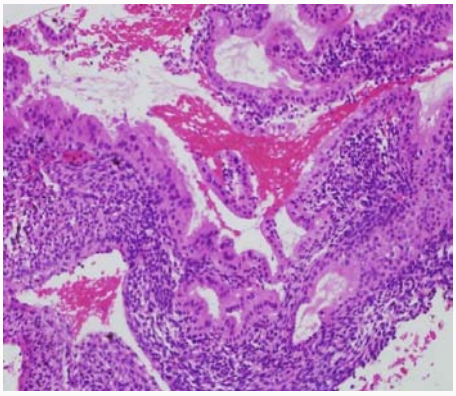

Figure 2: Post-treatment sample. Scarce glands and atrophic. The arrow indicates the most representative area of atrophic glands after treatment with progestins.

Thus, LNG-IUS was removed at 11 months after diagnosis, and it was decided, given the age of the patient, an ovodonation to achieve the best index of gestation. This is in line with the recently published European Society of Gynecological Oncology (ESGO) guidelines [2], stating that patients with previous infertility or risk factor of infertility should be referred and encouraged to consider ART. Actually, evidence shows that ART is a safe and effective procedure in this setting [3]. The preparation consisted in an inhibition with triptorelin depot prior to and subsequent endometrial estradiol transdermal preparation to have an endometrial thickness greater than 8 mm but with blood estrogen levels no greaterthan 200 pg /ml. Afterwards, endometrial maturation was made with micronized progesterone in high doses (800 mg / 24h).

Two embryos were transferred. Twelve and 14 days after embryo transfer, serial blood β-hCG assays showed a biochemical pregnancy. At 5 weeks from embryo transfer, a single viable pregnancy was detected at ultrasound. At 27th week the patient was admitted due to the threat of preterm labor. At 31 weeks + 4 days of gestation, two healthy male babies delivered by cesarean section by obstetric indication.

During cesarean section, multiple decidual biopsies for intraoperative frozen sections were performed (resulting negative), the abdomen was carefully inspected showing no macroscopic cancer spread and random peritoneal biopsies were also obtained. All definitive histological examinations of decidual, peritoneal, and placental biopsies resulted negative.

A total laparoscopic hysterectomy with bilateral salpingo-oophorectomy was performed four months after cesarean section. Histological examination of the uterus showed no areas of complex atypical hyperplasia or endometrial cancer. After 6 months of follow-up, the patient is free of disease.

Discussion

Endometrial cancer is the most common of the gynecologic malignancies [4]. Although it is primarily a disease of postmenopausal women, 25% are premenopausal and 3% - 5% are under age 40 [5]. Endometrioid adenocarcinoma, the most common type, is typically an estrogen driven disease affecting obese women.

Risk factors

Obesity and any condition that cause hyperestrogenic state are the main risk factors for endometrial cancer in young women [6].

A literature review, about fertility sparing treatment in young women with endometrial cancer, reported that the majority of patients had a history of anovulation, ovarian dysfunction, nulliparity and obesity [7].

Among young patients, thin women seem to have a more advanced stage compared to those who are obese. Duska [8], demonstrated that patients with BMI lower than 25 were more likely to have advanced disease and high-risk histology (uterine serous papillary, clear cell) compared with those women with a BMI over 25. Lee et al. [9] reported that young women who were obese, hypertensive and diabetic, tended to have well-differentiated tumours more frequently compared to whose patients without metabolic disease. A comparison of the disease in young and old-women is mandatory. The differences between two groups were exposed in the study of Setiawan et al. [10] and Colombo et al. [11].

The distribution of stage from I to IV and the histological type were similar, but grade I endometrial cancer seem to occur more frequently in young patients with less aggressive behaviour.

In this study, they demonstrated a higher prevalence of synchronic ovarian malignancies in the younger group. The higher prevalence of synchronous ovarian cancer in younger women is demonstrated in several studies. Walsh [12] reported a rate of 25%, while Gitsch [13] reported a rate of 29%.

In addition to this, young women with endometrial cancer should always be carefully consulted about the need for a genetic test for detection of Lynch syndrome, depending either on their family history of cancer or depending of testing for mismatch repair protein expression using microsatellite instability testing and immunohistochemistry analysis. This will alert and identify patients with Lynch syndrome who need a very close monitoring and tailored consultation about their further follow-up and management. It is debatable whether a patient with Lynch syndrome should be candidate to conservative management.

Extensive counselling of the patient is the integral part of the management. The detailed information about all aspects and risk of conservative treatment has to be provided and informed consent obtained, before initiation of the treatment.

Patient selection

The selection of endometrial cancer patients for whom fertility-sparing treatment is appropriate is the aim to achieve the best

outcomes. All relevant studies recommended for patients with early-stage, well-differentiated, endometrioid type endometrial adenocarcinoma with no evidence of myometrial invasion or extrauterine spread. According to the International Federation of Obstetrics and Gynecology (FIGO) staging system, stage IA (confined to endometrium), grade 1 endometrioid adenocarcinoma cases are eligible for fertility-sparing treatment.

Well-differentiated tumours have a very low risk of myometrial invasion and extrauterine spread (lymph node, ovarian or peritoneal metastasis). In addition to this, well-differentiated tumour cells express more progesterone receptors and therefore respond to progesterone therapy [14].

In the other hand, the absence of myometrial invasion is also important clinical aspect of endometrioid adenocarcinoma, because implies a very low risk of extrauterine disease.

Navarria et al. [15] reported the estimated number of patients who may need fertility – sparing treatment is a based population as a rate of 0.3 in 100.000 women of these criteria.

However, because the incidence of young women with endometrial cancer is increasing and the number of women who want to delay having children, the future need for fertility – sparing treatment will increase.

Management

Although hysterectomy represents the standard treatment for endometrial cancer, it is often not accepted when the patient is young and desires a pregnancy in the future.

In these cases, a fertility-sparing treatment could be offered as an alternative option to accurately selected patients. Hormonal therapy alone or combined with endometrial ablation by hysteroscopy are identified in literature as the most used and effective conservative treatments. However, patients must be informed that data about medical treatment are incomplete because of the limited number of treated patients and that there is a risk of disease progression during treatment or after initial response. Both oral and intrauterine hormonal treatment are reported in literature [16].

Saegusa [17], suggested the use of progestins when positive progesterone receptors are detected in well differentiated endometrial cancer. Medroxyprogesterone acetate (400 mg/ day) and megestrol acetate (160 mg / day) were the more frequently progestins used for oral treatment.

Ricciardi [18] reported a study of 15 patients enrolled from May 2003 to December 2009 with early stage endometrial cancer or atypical hyperplasia treated conservative therapy (medroxyprogesterone acetate 500 mg/day - 1000 mg/day or megestrol acetate 80 mg/day - 160 mg/day) used for at least 12 weeks. The follow-up was performed by hysteroscopic biopsy after one month starting the treatment, and then repeated every three months until delivery. After delivery, the follow-up was performed at 4, 8 and 12 months by hysteroscopic biopsy. Of 15 women, 11 had complete remission and 4 of them attained pregnancy with 4 live births. Three patients manifested disease progression and received definitive surgery and one did not have any response to treatment with further hysterectomy.

Mentrikoski [19] in a prospective study, assessed the outcome of 30 women aged between 18 and 42 years, with complex atypical hyperplasia and grade I, stage IA endometrial cancer conservatively treated. Megestrol acetate (40 mg/day - 160 mg/day) was administered and continued for 3 months. 23 women (77 %) had complete response, persistence in 3 cases (10%) and progression in 4 cases (13%). The mean to regression was 7.5 months in premenopausal women and 6.8 months in postmenopausal women. No significant difference was noted in resolution status between pre- and postmenopausal women.

Yamazawa et al. [14] in a prospective study from 1999 to 2005, assessed the outcome of nine women aged between 28 and 40 years, with grade I, stage IA endometrial cancer conservatively treated. All patients received progestins (medroxyprogesterone acetate 400 mg / day) continued for 6 months. Seven women had complete response and two of nine patients partially responded to treatment. Two patients developed recurrent disease 10 and 22 months after the last control (25% recurrence). In addition to this, of eight patients who sought conceive, four had a pregnancy and three of them delivered. The other aim of this study was to predict complete response investigating expression pattern of five markers (IGF1R, PTEN, progesterone receptor, estrogen receptor and ki67). This study conclude that progesterone receptors are reliable markers to predict complete response of endometrial cancer.

In a more recent experience, Chen [20] performed, between January 2000 and December 2011, a retrospective study evaluating the outcome of 53 patients with endometrial carcinoma, stage IA, who underwent conservative treatment with progestin (medroxyprogesterone acetate (MPA) at doses of 250 mg/day - 500 mg/day or Megestrol Acetate (MA) at doses of 160 mg/day – 480 mg/day. This study demonstrated the feasibility of fertility-sparing strategies in women of childbearing age with Progesterone Receptors (PR)- positive. Also, concluded that to decrease the risk of EC recurrence, the identification of relevant factors that predict treatment success is necessary. Obese patients (BMI ≥30) had a lower Complete Remission (CR) rate to progestin treatment, and practitioners should be particularly concerned about weight reduction in these patients. In patients without a histologic response to progestin after 12 months, the mode of therapy should be revaluated; these patients should be counselled on the increased probability of failure.

Several studies are available in literature about progestin-releasing IUD, as an alternative option to oral administration in the conservative management of endometrial cancer. There are several progestin-releasing IUDs, but the IUD that has been studied most commonly for EC treatment is LNG-IUD that releases levonorgestrel 20 mcg/day (LNg20; Mirena). Progestin IUDs may be used for treatment alone or in combination with an oral progestin.

In 2004, Montz [21] in a prospective study from 1999 to 2003 intrauterine progesterone appears to eradicate some cases of presumed stage IA, grade 1 endometrioid cancer.

Cade [22] reviewed his experience of all patients receiving intrauterine progesterone therapy for stage-1 endometrial cancer. Of the 16 patients investigated, 10 patients (63%) responded to treatment, with a median time to response of 5.5 months and the other 6 patients did not respond to treatment, but all were either early in treatment or opted for surgical management before the average time of response. Kim et al. [23], in 2012 demonstrated that intrauterine progestin (Levonorgestrel) could be used in combination with oral medroxyprogesterone in the conservative treatment of endometrial cancer. Four of five treated patients and one of them had complete and partial response respectively. All women had early stage disease

and follow-up lasted from 6 to 16 months.

A new fertility-sparing approach has been proposed in three recent papers. Mazzon [24], included six patients with grade I, stage IA endometrial cancer with positive progesterone receptor underwent resectoscopic eradication of the lesion, ablation of the closer endometrium and the underlying myometrium. After hysteroscopy, all patients started oral progestins (megestrol acetate) for 6 months. All patients had complete remission and four of them achieved pregnancy.

Arendas [25] described two cases of stage IA endometrial cancer managed conservatively by a combination of hysteroscopic surgery and medical therapy for fertility-sparing purposes. One of which achieved successful pregnancy using assisted reproductive technology. They reviewed the existing literature on the use of hysteroscopic resection in conservative management of endometrial cancer to preserve fertility and concluded that hysteroscopic resection to conservative management of early-stage endometrial carcinoma may be a way to improve response and recurrence rates in women wishing to preserve fertility.

Falcone [26] included 28 women, aged 18 to 40 years with early stage of endometrial cancer. Hysteroscopic Resection (HR) was performed to remove the tumour lesion, the endometrium adjacent to the tumour, the myometrium underlying the tumour. If final pathology confirmed a G1 endometrioid EC with no myometrial invasion and PR positivity at immunohistochemistry, hormone therapy was started 1 week after HR. Adjuvant hormonal therapy consisted of oral progestins (megestrol acetate) or intrauterine progestin device for 6 months. A complete response was observed in 96.3% of the patients 85.7% of patients achieved a durable complete response, with a median duration of 95 months.

Follow up during conservative treatment

Although today no clear guidelines about follow-up for women who undergo conservative treatment have been expressed, most authors consider performing the first endometrial biopsy after three months of hormonal therapy and then every three months until 24 months.

Chiva et al. [27] reported that a follow-up with endometrial evaluation should be taken after 12 weeks of treatment. When a positive biopsy occurs, another biopsy should be performed after 24 weeks of treatment. If the second biopsy results positive, a radical treatment should be carried out. If the second biopsy results negative the patient could start to attempt conception. Endometrial sampling could be taken every 3 months.

Eskander et al. [28] suggested an endometrial evaluation with curettage after three months of treatment. In case of disease progression or persistence of cancer, he recommended hysterectomy. If response to conservative management is confirmed, hormonal therapy should be continued for 6 to 9 months.

Chen et al. [20] proposed a strict follow up with endometrial evaluation 3 months after initiation of progestin treatment. Then it recommended hysteroscopic and histologic evaluation every 3 months until 12 months. In addition to this it considered the identification of relevant factors that predict treatment success is necessary. Obese patients had a lower CR rate to progestin treatment, Also, patients without a histologic response to progestin after 12 months, the mode of therapy should be revaluated; these patients should be counselled on the increased probability of failure.

Falcone [26] recommended three months after starting progestin therapy, patients entered the follow-up phase undergoing: 3-monthly general and gynecological examinations, transvaginal ultrasonography (TVS), serum cancer antigen 125 (CA-125) and diagnostic hysteroscopy with endometrial sampling.An abdomen-pelvis Computed Tomography (CT) is performed at 6 months and 6-monthly thereafter.

Definitive treatment after conservative treatment

Several authors suggested to performhysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomywhen patients have completed their fertility plans. A small risk of disease progression after or during conservative treatment is described, therefore hysterectomy should be considered after pregnancy. In addition to this, for the high rate of synchronous ovarian cancer it is recommended to complete the surgery with bilateral salpingo-oophorectomy [16,27].

In 2012, Gallos [16] published a meta analysis of 32 studies of women with endometrial cancer managed with fertility-sparing treatment. He found a regression rate of 76.2% and a relapse rate of 40.6%. He concluded that because of the high rate of recurrence after successful fertility-sparing therapy prophylactic hysterectomy with bilateral salpingo-oophorectomy is the best option for patients who have completed family planning [29,30].

Conclusions

Even though endometrial carcinoma is mainly diagnosed after menopause, it may occur in young women as well and anytime a young woman complains abnormal bleeding, endometrial carcinoma should be ruled-out and all diagnostic tools should be used to exclude the pathology. This is particularly important if risk factors for endometrial carcinoma are present. This subject is important as the number of younger women with endometrial cancer is rising because of increasing obesity. The standard treatment for endometrial cancer is total hysterectomy. In recent years, the surgical management of the majority of endometrial cancers has become less extensive. Hysterectomy removes the primary source of the cancer and allows the assessment of the degree of local invasion. The ovaries are removed to eliminate a source of estrogen, and to remove metastatic or synchronous tumours. The role of lymph node dissection is controversial. Although this procedure is usually performed in women in menopause, conservative treatment could be a reasonable option to propose to young patients with stage IA grade I endometrial cancer and endometrial hyperplasia who desire to retain fertility. An exhaustive evaluation of grade, stage, histology type, hormonal receptors expression, myometrial invasion and metastatic diffusion is necessary before introducing hormonal therapy as alternative treatment. Today most of controlled studies about the conservative treatment concerns patients with endometrial hyperplasia and endometrioid adenocarcinoma grade I. Translation research in EC cell lines has very recently yielded very interesting results regarding the use of the antidiabetic drug metformin and its effect on EC cells. These studies have shown that metformin suppresses EC cell growth and exhibits an antiproliferative effect in women with EC and insulin resistance. A prospective phase II study is announced and will further elucidate the role of metformin in combination to progesterone and active weigh management for the treatment of early stage EC in the future.

There is often a debate when cancer is diagnosed in young patients who wants to preserve fertility: risks and benefits of conservative treatment should be widely discussed with patients. We conclude, that nonsurgical approach is a valid option but indications and eligibility of different therapies must be carefully considered and strictly followed.

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