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Fertility-sparing treatment of endometrial cancer precursors among young women: a reproductive point of view

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Abstract. – BACKGROUND: Early-stage endometrial cancer and complex atypical hyperplasia are treated with hysterectomy and bilateral salpingo-oophorectomy. An emerging issue among younger women affected is the possibility of a fertility-sparing treatment with progestative therapy and close follow-up.

AIM: To assess the possibility of conceiving after a diagnosis of atypical endometrial hyperplasia among women younger than 40 years old, in term of delaying definitive treatment and achieving pregnancy

MATERIALS AND METHODS: 15 women younger than 40 years old with complex CAH or early carcinoma of the endometrium and a wish to preserve fertility. Progestins were administered orally for at least a 12 weeks period. Endometrial biopsies were used at follow-up.

RESULTS: In 11 women, a complete pathological remission of the disease was observed. 4 pregnancies were attained in 4 women. 3 showed progression and underwent definitive surgery at 18 months. 1 showed no response at 24 months and 3 cycles and was counseled to receive a hysterectomy.

CONCLUSIONS: A conservative approach in patients younger than 40 years appears a valid option, and a progestative therapy trial should be attempted whether a valid consensus is attained. Considering the risk to find AEH at biopsies and eventually a carcinoma at hysterectomy (25% of cases) a careful management is strictly required.

Key Words:
Endometrial Cancer, Pregnancy, Atypical hyperplasia, Progestin.

Introduction

Early-stage endometrial cancer is treated with hysterectomy and bilateral salpingo-oophorectomy. An emerging issue among younger women affected is the possibility of a fertility-sparing treatment. Several case reports have been published thru the last years in literature. Most of them considered progestative therapy as a more than valid option. Unfortunately, these reports did not change protocols followed routinely. The major risk of conceiving after endometrial cancer or complex atypical hyperplasia (CAH) is still delaying a definitive treatment. Hence, not only endometrial cancer but also complex atypical hyperplasia are currently treated by hysterectomy as main option in many centers, fearing the well-known 29% progression rate as described by Kurman et al[1].

In addition, we would like to take into account some considerations about the most effective method of achieving a pregnancy (if there is one) as well as focus on proper pregnancy-related risks. Reporting our case load, we tried to discuss issues stated above and to present some follow-up results.

Materials and Methods

Patients aged 18 to 40 years old with a diagnosis of early-stage endometrial cancer or CAH, desiring a conservative treatment in order to achieve a pregnancy, were counseled and considered eligible to the study.

15 patients were enrolled from May 2003 to December 2009 at our University Center.

Inclusion criteria required a histologically proven diagnosis of endometrial hyperplasia with atypia or a G1 carcinoma, without myometrial invasion at MRI or US. Exclusion criteria were a histological diagnosis of clear cell, papillary serous, endometrioid endometrial carcinoma, an MRI showing no evidence of extrauterine spread or myometrial invasion, absence of US findings suspicious for ovarian malignancy, unclear endometrial primary or recurrent endometrial can-

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cer, a history of a previous thrombotic event, known thrombophilic condition or poorly controlled diabetes, a history of breast cancer or other hormonally responsive malignancy, uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations.

Preoperative CA-125 was collected in all patients.

Progestin therapy consisted of megestrol acetate (80-160 mg/daily) or medroxyprogesterone acetate (500-1000 mg/daily) for at least 12 weeks.

Endometrial histology was assessed one month (4 weeks) after completion of therapy and then obtained every 3 months as follow-up. Endometrial cytology and transvaginal US were routinely performed after remission and parturition. Biopsies were collected at 4, 8 and 12 months after parturition in all patients who underwent a full term pregnancy. Outpatient hysteroscopy was the chosen method of collecting biopsy specimens.

Results

14 women had a previous diagnosis of CAH and 1 a well-differentiated adenocarcinoma.

This latter was given as a stage IA G1 with endometrioid differentiation, after review by a senior pathologist.

11 women were nulliparous; of which 2 have had at least one previous spontaneous abortion. One woman was gravida 2 para 1 including a tubal pregnancy. One was gravida 1 para 1.

Mean age at diagnosis was 32 years with a median of 30 (range 25-40 years).

Up than a half of the patients (9 out of 14) referred primarily to ART (Assisted Reproductive Technology) centers with infertility as initial complaint. Only a few had previous irregular vaginal bleeding as a symptom leading to physician examination.

Commonly associated conditions were chronic ovulation disorders such as PCOS (polycistic ovary syndrome) or chronic anovulation linked to history of infertility in 13 women. One woman had chronic hypertension related to renal disease.

3 women received definitive surgery after 18 months. 1 patient underwent removal of the corpus uteri after 24 months and no response after undergoing 3 cycles of progestin.

11 women showed remission of disease.

In 4 cases a pregnancy could be eventually achieved and biopsies specimen after parturition showed complete remission. Pregnancies were all attained after IVF (*in vitro* fertilization), 3 performed on spontaneous cycle, one with ovulation induction (using Clomiphene citrate). Time to pregnancies was 6, 7, 12 and 15 months.

CA-125 resulted pre-operatively < 35 UI/mL in all patients.

Discussion

A conservative approach to endometrial cancer or CAH is well supported by literature evidences. Specifically, progestative therapy is been considered effective and safe in this group of patients.

Efficacy showed in early-stage endometrial cancer is clearly superior to the one found in palliative care of recurrent or advanced carcinomas. Response rate of 57% to 75%, as reported by Gallup and Stock[2] for early-stage, compare to 20% to 40% seen in advanced or recurrent cases according to Jeyarajah et al[3]. This relates to hormonal status. It is well documented that EC (endometrial cancer) in younger women has a better prognosis. Response to progestins seems highly dependent on hormonal receptor status; a study by Shabani et al[4] demonstrated how this relates closely to PR distribution on the sample. In the carcinoma subset, G1 lesions show a higher rate of ER and PR receptors (85%-90%) comparing to G2 and G3 tumors (55%-60%). One of the cases reported showed no response to conservative hormonal therapy and, eventually, progressed to a higher stage. However, it is not yet clear how to assess priory a responder from a non-responder or which drug should be more appropriate to specific cases. Answers to these questions would come only from larger studies, focused on identifying molecular markers, which are currently missing.

Duration of progestative treatment in our study followed a protocol of at least 12 weeks of treatment with control biopsies collected one month after completion. Progestins were furthered in cases that showed no response at first cycle. Randall et al[5] found that total duration of treatment range from 3 to 24 months. In our study, it ranged from 3 to 24 months with controls every 3 months. Nevertheless, we had only one case whether treatment was furthered until 24 months. Still, no response could be obtained.

A different approach was used for endometrial carcinoma compared to CAH. It is clear to date that CAH on biopsy specimens comes from a uterus that harbors a carcinoma, which could be eventually seen at hysterectomy in the 25% of cases. Moreover, it is not always quite easy to distinguish CAH from well-differentiated endometrial carcinoma at pathology specimen. This is to underline the needing of a correct diagnosis and assessment of disease extension.

Hysteroscopic-targeted biopsies and a careful pathologic evaluation of the specimen are mandatory. In the event of endometrial cancer, MRI or TV-US are claimed to assess extent of myometrial invasion. Recently, an interesting case report from Mazzon et al[6] showed an alternative method to conserve fertility in these patients. Hysteroscopic resection of the tumor lesion with a wider excision including underlying myometrium allows the pathologist to assess margins. Tumor excision with clear margins addressed patients to follow-up, positive lateral margins to hormonal therapy, positive deep margins to hysterectomy.

IUD (intrauterine device) releasing progestin is another option that seems promising in offering control of the disease, but it is not indicated in women seeking pregnancy therefore it was not considered in the current study. Moreover, we are concerned about the follow-up of this subset of patients limited by the obstacle of collecting biopsy specimens.

Role of ART in these patients is not only considered to implement the chance of a pregnancy but even to shorten the time to achieve a pregnancy. Pregnancy itself is certainly a highly effective treatment, with the endocrine placenta as a natural continuous progestin source. The rarity of endometrial cancer reported during pregnancy is a further evidence of conditions that hardly co-exist.

The risk of co-existing synchronous ovarian cancer is well stated in the literature and it should be always taken in account, most likely in non-responders a suspicion should be raised. Younger women are more likely to present this association compared to older women. Gitsch et al[7] reported a 29% rate, Evans Metcalf et al[8] 11%, whether a more recent report by Walsh et al[9] suggested a 25% of chances. It is interesting to note how an Italian study by Signorelli et al[10] considered laparoscopic staging and CA-125 in the work-up of these patients. Still, they reported 2 undetected intra-parenchymal ovarian cancers among their population study. These findings overstate careful management in attempting conservation of fertility in this subset.

Follow-up was attained performing serial biopsies. Hysteroscopy was preferred to sample the endometrium. A limit of D&C (dilation and curettage), considering the final target, is the frequent appearance of uterine synechiae, a well-known cause of infertility. Hysteroscopy allowed assessing the cavity, to perform adhesiolysis whether it appeared useful and to attain more representative samples.

Use of ART ovulation induction drugs raise some concerns about high level of estrogens released in these patients, which potentially represent a risk. No evidence of a higher risk of endometrial cancer with ovulation induction can be found in literature. Our study showed a safe outcome for a woman treated with clomiphene citrate before administering a progestin.

Several studies report an association between PCOS and endometrial cancer. Anovulatory women may be similarly exposed to a higher risk of cancer. This accords to the hypothesis that the stimulatory effect of estrogen, when unopposed by progesterone, induces endometrial carcinogenesis. This association is more likely to exist among younger women. In a study by Pillay et al[11], PCO (as a marker of PCOS) were similarly prevalent in women with EC (8.6%) and benign controls (8.4%); however, in women aged < 50 years, PCO were more prevalent in women with EC (62.5 versus 27.3%, $p = 0.033$). The MD Anderson study by Schmeler et al[12] showed that a high proportion of young normal-weight women with EC were nulliparous, had a history of infertility, irregular menstrual cycles and synchronous tumors of the endometrium and ovary when compared to the general population. An unsolved question is whether EC in this population would show a better prognosis as some have stated or not. Evidences from protein expression studies show that a possible pathway for endometrial carcinogenesis in PCOS involves cyclin-D1. This understates the idea of an improved EC prognosis in women with PCOS and aligns it to the same of general population.

Conclusions

Our data suggest that the risk of developing endometrial carcinoma was lower in women treated with progestins within 8 weeks of their atypical hyperplasia diagnosis than in women untreated.

The choice of attempting a conservative treatment with progestative therapy in women who had a diagnosis of CAH relates mostly to the effective risk of cancer progression.

Patient selection is probably of most important concern. Considering the lack of evidences in the current knowledge, potential risks underlying the choice of a trial with progestin should be considered.

Probably, the risk of progression to carcinoma during a trial is not a main concern whether the concurrency of a carcinoma in women with CAH diagnosis should not be underestimated. Data show that women who had a hysterectomy in the 12 month period following a CAH diagnosis had a carcinoma in the 46% of cases[13,14]. Even more important than diagnostic accuracy is the therapeutic response to progestin therapy. A median response was achieved at 12 months, 3 women recurred at 18 months, 1 did show no response; All of them received hysterectomy. Close follow-ups are essential for these patients to assure safety and detect promptly a progression or a recurrence. Assisted reproduction techniques did not show any negative impact on the prognosis and pregnancy itself resulted curative in all cases.

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