

Endometrial Adenocarcinoma in PCOS

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ABSTRACT

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Endometrial cancer refers to several types of malignancy which arise from the endometrium or lining of the uterus. Endometrial carcinoma usually occurs in women above 40 years of age and presents as abnormal vaginal bleeding. Even though literature says, endometrial carcinoma rare in young females both of our females in their prime age succumbed to malignancy. The incidence varies widely throughout the world. It is the most common invasive tumor of the female genital tract in the U.S. and is decreasing in frequency in women in their 50s in whom it is related to unopposed estrogen stimulation. In developing countries, the incidence is four to five times less. Worldwide, it is the fifth commonest cancer in women. Clinical behavior of endometrial adenocarcinoma depends on the histologic type, the grade (degree of differentiation) and the stage (extent of spread). Endometrioid carcinoma has a better prognosis than the other histologic types, which tend to occur at a higher stage

Patients with endometrial cancer who have localized disease are usually curable by hysterectomy and bilateral salpingo-oophorectomy. Best results are obtained with either of two standard treatments: hysterectomy or hysterectomy and adjuvant radiation therapy

Keywords: Endometrium, PCOS, Endometrial carcinoma

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INTRODUCTION

Endometrial cancer refers to several types of malignancy which arise from the endometrium or lining of the uterus. Endometrial carcinoma usually occurs in women above 40 years of age and presents as abnormal vaginal bleeding. It is very rarely seen in a young woman. We present two cases of endometrial carcinoma in a young infertile woman. The median age of patients with endometrial cancer is 61 years with 75 - 80 % of women being postmenopausal and only 3-5% being less than 40 years.¹ The younger women with endometrial carcinoma tend to be obese and suffer from chronic anovulation. The diagnosis is usually made in a routine course of investigations for infertility or irregular vaginal bleeding. Risk factors include obesity, estrogen therapy, nulliparity (as a result of infertility due to chronic anovulation), chronic anovulation, late menopause, hypertension, diabetes, tamoxifen therapy, and high socioeconomic status.

An association between polycystic ovary syndrome (PCOS) and endometrial carcinoma was first suggested in 1949. Since then, several studies have been published that appear to support this association, and it is common practice among gynecologists and physicians to prescribe hormonal treatment to reduce this perceived

risk, although there is no consensus as to the subgroup of PCOS in whom this is required.^{2,3} The mechanism(s) underlying any association are also unclear, but it is again widely assumed that chronic anovulation, which results in continuous estrogen stimulation of the endometrium unopposed by progesterone, is a major factor. However, obesity, hyperinsulinemia, and hyperandrogenism, which are also features of PCOS, are risk factors for endometrial carcinoma, but it does not necessarily follow that the incidence or mortality from endometrial cancer is increased in women with the syndrome.

In estrogen-related conditions, endometrial cancer most likely progresses from endometrial hyperplasia, tends to be well differentiated, and is associated with a generally favorable prognosis. In other conditions with unknown cause, the cancer typically develops de novo in the setting of an atrophic or inert endometrium, tends to have more aggressive or undifferentiated cell types, and usually has a poorer prognosis than do the estrogen-related endometrial carcinomas. Nearly 50% of these women who are under 40 years are nulliparous and more than 75% of them are obese. Endometrial adenocarcinoma manifests as abnormal vaginal bleeding. The standard treatment for endometrial carcinoma is total abdominal hysterectomy with bilateral salpingo-oopho-

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rectomy unless the tumor is extremely widespread or the patient is medically unfit for surgery. The gynecologist is in a dilemma when treating a young woman with endometrial carcinoma who wishes to preserve fertility. Recently we met with two cases of endometrial adenocarcinoma in young infertile females. The particular clinical scenario is discussed. Case history 31 year old Mrs. S. approached our centre about 2 yrs back for primary infertility evaluation. She was married for 4 yrs. Her menstrual cycles were regular with no relevant h/o of medical or surgical illnesses in the past. She was an average built lady of BMI 23 kg /m2. All her basic hematological, hormonal and sonological evaluations were within normal limits. Mr. S was found to have mild oligoasthenospermia. They were anxious enough to have a baby. We put her on ovulation induction with clomiphene citrate combined with IUI for 4 cycles. During her routine follow up she was found to have endometrial hyperplasia (Figure 1).



Figure 1. USS picture showing Endometrial hyperplasia

Operative lap hysteroscopy was done in Nov 2006 which revealed features of mild endometriosis. On finding suspicious nodular deposits over ovary, biopsy was taken. Endometrium as expected earlier was found unusually hyperplastic and same was also biopsied. The histopathological report came as endometrioid adenocarcinoma of endometrium and ovary. Considering the rarity second opinion taken from an oncology centre came as endometrial hyperplasia with extensive squamous / morular metaplasia/ endometriotic deposits over ovary and hence they advised close follow up. Based on this we advised her to take continuous progestogen therapy and follow up every 3 months. Unfortunately she did not turn up for regular follow up. She reported to us back after 6 months with h/o irregular bleeding per vaginum by April 2007. Then her transvaginal sonographic and hematological evaluation findings were reassuring. Hence she underwent one cycle of COH with aromatase inhibitors combined

with IUI. Again follow up was lost and reported by February 2008 with h/o irregular bleeding per vaginum. The then transvaginal sonography showed a hyperplastic endometrium with increased vascularity and thickened endometrium of 23 mm size (Figure 2).

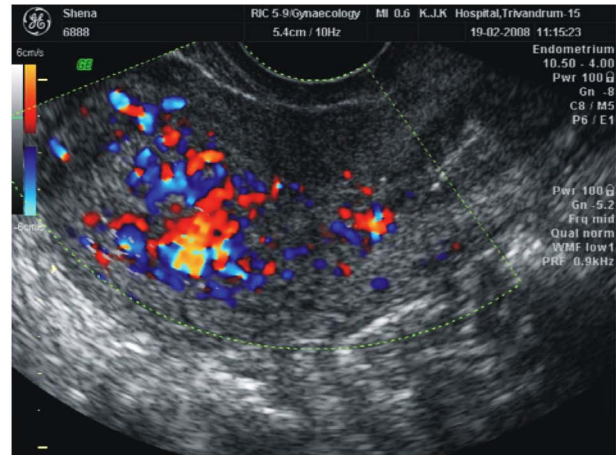


Figure 2. 3-D Doppler showing increased vascularity

Second opinion from an oncology centre in Spain gave the report as low grade little aggressive adenocarcinoma with early invasive features and advised us to proceed with simple hysterectomy. Moreover they could not find a normal endometrial area favouring implantation. There ends all her hope for fertility (Figure 3).

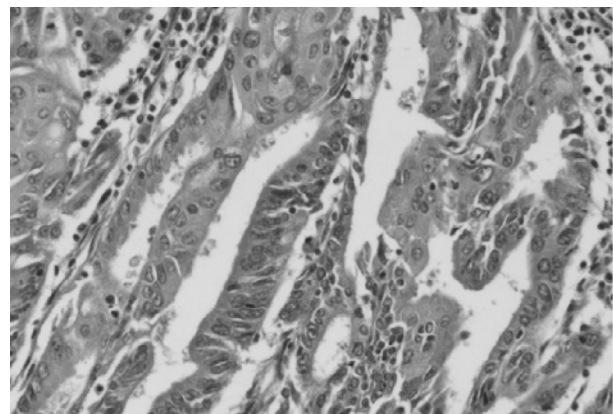


Figure 3. Endometrial curettings showing endometrial hyperplasia and intra endometrial adenocarcinoma.

Another lady Mrs. J 32 year old reported to us about 4 years back for primary infertility evaluation. She had c/o irregular cycles and was a c/o P COD. Of course she underwent ovulation induction with ovulogens like clomiphene citrate, aromatase inhibitors and gonadotrophins for few cycles. Meanwhile she developed irregular bleeding per vaginum by March 2008. On evaluation found to have thickened endometrium, and endometrial sampling detected well differentiated adenocarcinoma endometrium. She also ended up in hysterectomy.

DISCUSSION

Eventhough literature says, endometrial carcinoma rare in young females both of our females in their prime age succumbed to malignancy. The incidence varies widely throughout the world. It is the most common invasive tumor of the female genital tract in the U.S. and is decreasing in frequency in women in their 50s in whom it is related to unopposed estrogen stimulation. In developing countries, the incidence is four to five times less. Worldwide, it is the fifth commonest cancer in women. Clinical behavior of endometrial adenocarcinoma depends on the histologic type, the grade (degree of differentiation) and the stage (extent of spread). Endometrioid carcinoma has a better prognosis than the other histologic types, which tend to occur at a higher stage. Staging is based on degree of myometrial invasion, cervical, adnexal and adjacent pelvic organ invasion, result of peritoneal fluid cytology and distant organ metastasis. Lymph node status is an important prognostic factor. 75% of patients present with stage I disease and these have 95% 5-year survival. Those tumors associated with unopposed estrogen tend to have low histologic grade and clinical stage, hence tend to have better prognosis. These usually occur in young women.

Patients with endometrial cancer who have localized disease are usually curable by hysterectomy and bilateral salpingo-oophorectomy. Best results are obtained with either of two standard treatments: hysterectomy or hysterectomy and adjuvant radiation therapy (when deep invasion of the myometrial muscle [50% of the depth] or grade 3 tumor with myometrial invasion is present). Results of two randomized trials on the use of adjuvant radiation therapy in patients with stage I disease did not show improved survival but did show reduced loco regional recurrence with an increase in side effects. In young women with low histological grade and early stage disease conservative hormonal therapy has been tried with close follow-up. There are reports of high dose medroxyprogesterone acetate (600mg/day) treatment with endometrial evaluation every 3 months to evaluate the effects of medication.⁴ Whenever the response has not been satisfactory, hysterectomy is advocated. For a successful outcome following conservative approach, a strict clinical staging in the form of physical examination and imaging with ultrasound, CT or MRI and a cautious evaluation of histological grading by a pathologist are required. This is then followed by at least 6 months of progestogen therapy and evaluation of response by endometrial sampling.^{5,6} We did not consider conservative management

with progestogen in our patient second time for the following reasons. Since the conversion of hyperplasia to frank malignancy was fast in her case. And also due to her poor compliance.

Large-scale studies of morbidity and mortality in unselected populations of women with PCOS are needed. Women with PCOS are increasingly aware of the possible risks, and it will be necessary to identify which of them, if any, are at increased risk and how this risk can be effectively reduced. These clinical situations are not only rare but also unfortunate.

CONCLUSION

Carcinoma endometrium should be kept in mind while evaluating young women with PCOS for abnormal uterine bleeding. Only strictly selected patients should therefore be indicated for long-term progestogen treatment and careful evaluation before and after treatment should be performed.

END NOTE

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Conflict of Interest: None declared

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