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Fertility Sparing Options in Gynecologic Oncology

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Introduction

Traditionally, and according to actual guidelines, [1] cancers affecting female genital organs are treated with radical surgery, chemotherapy, radiation therapy or a combination of the above mentioned, all bearing a permanent damage of the female reproductive tract. Anyway, facing with a continuous trend in postponing childbearing and the early detection of gynecologic cancers, there has been a vast increase in the number of patients seeking fertility preserving options for the treatment of gynecologic malignancies [2]. Of the 6.6 million cancers occurring worldwide in female population, 1.09 million (16%) affects the female genital organs and up to 20% will be diagnosed in women of reproductive age. [3,4] As many as 15-45% of cervical cancers, 5-29% of endometrial cancers, and 12-34% of primary ovarian malignancies will be found in women eligible for fertility preservation. It is not surprising so the increase interest in oncofertility discipline. Even if not yet considered as "standard treatments", there are continuously emerging data on fertility sparing options available in gynecologic oncology. In the present paper we briefly review current options for women desiring fertility-sparing treatment of gynecologic malignancies [5].

Cervical Cancer

For women with stage IA1 cervical cancer (non-visible lesion invading < 3 mm), coldknife-conization, loop-electrosurgical-excision-procedure (LEEP), or CO2-conization are all reasonable options. Recurrence after these procedures are <1% assuming negative margins are achievable.

For stages IA2 (non-visible lesion invading 3-5 mm) or IB1 (non-visible lesion invading > 5 mm or any visible lesion < 4 cm in size) disease, options vary depending on tumor size, histology, depth of invasion, and the presence or absence of lymph-vascular space invasion. Radical trachelectomy (via open, laparoscopic, robotically-assisted or vaginal approaches) plus pelvic lymphnode dissection is a largely accepted treatment for young women with early cervical cancer desiring fertility-sparing surgery. Typically this procedure is offered to women with squamous or adenocarcinomas less than 2 cm in size, however many centers are undertaking larger lesions with successful outcomes. The 4% recurrence rate after radical trachelectomy is seemingly equivalent to recurrence after radical hysterectomy and pregnancy rates of 41-79% have been reported. There is a slight increase in second trimester miscarriage but the majority of pregnant women deliver after 34 weeks. To overcome the increased risk of pre-term birth and second trimester miscarriage, less radical procedures such as cervical conization or simple trachelectomy with pelvic lymphadenectomy or neoadjuvant-chemotherapy followed by cervical conization and lymphadenectomy are also being explored for stages IA2/IB1 disease. Even if largely limited to small series, comparable results in terms of oncological and obstetrical outcome seem achievable [6-8].

Endometrial Cancer

Conservative therapy using oral/injectable progesterone therapy or a progesterone eluting IUD for uterine cancer should be limited to grade 1 endometrioid adenocarcinomas without myometrial invasion. Although evaluating myometrial invasion is difficult, pretherapeutic MRI/ Transvaginal ultrasound are often obtained to rule out significant invasion. Exclusion of adnexal masses is mandatory being the risk of adnexal involvement or presence of synchronous tumors up to 25%. In assessing outcomes, the published literature is largely composed of small case series with reported response rates of 75-80% and recurrence rates of 20-40%. Pregnancy rates as high as 35% have been achieved. Pretreatment dilatation and curettage ± hysteroscopy for accurate assessment of cell histology and grade is a necessity as well as close treatment monitoring with frequent endometrial sampling [9-11].

Ovarian Cancer

Ovarian cancer is a heterogeneous group encompassing various types of diseases with different histologies, treatments and prognosis.

Due to their exquisite sensitivity to chemotherapy, germ-cell tumors of the ovary are highly amenable to fertility sparing therapy. Even when gross tumor on the bilateral ovaries and uterus are encountered, performance of a unilateral salpingo-oophorectomy (largely for diagnostic purposes) with retention of the diseased contralateral ovary and uterus followed by chemotherapy is a widely accepted practice. Overall germ-cell tumors have a cure rate of 90-95%, and a pregnancy rate of 35%.

Borderline tumors of the ovary as well as grossly apparent stage I sex-cord stromal tumors can also be managed with a unilateral salpingo-oophorectomy only or even cystectomy if feasible. Data over 2500 borderline tumor patients treated conservatively are available with a pregnancy rate as high as 55%.

For invasive epithelial ovarian cancer grossly limited to one ovary, conservative staging sparing one ovary and uterus ± adjuvant chemotherapy is an option in well consented patients. To date, more than 800 cases of early stage epithelial ovarian cancer managed with unilateral salpingooophorectomy have been reported with a recurrence rate ranging from 8 to 17% and 36% of patients achieving pregnancy. Apart patients with FIGO stage IA G1-2 for whom fertility sparing treatment is largely accepted; only few data for higher stages or aggressive histologies are available. Anyway comparable oncologic and obstetrical results seem achievable [12-17].

Oncofertility

Major exciting advances have been made in reproductive-endocrinology and infertility with respect to embryo, oocyte, and even ovarian tissue preservation in young women with a diagnosis of cancer at any site (not just gynecologic malignancies). Those new technologies extremely appealing especially when dealing with malignancies other than that of the female genital tract can find a place even in a gynecologic oncologists' practice. It is well known that endometrial cancer patients as well as patients suffering from borderline tumors frequently have a history of infertility. To date ovarian stimulation after conservative treatment for cervical, endometrial and even borderline ovarian cancer is considered acceptable and is under investigation in other gynecological malignancies [18].

Conclusions

In the last 20 years, gynecologic oncologists have developed a wide variety of fertility- sparing therapies for young women with gynecologic malignancies. These non-standard treatments are best administered and managed in referral centers and on-study when appropriate. Careful patient selection and extensive discussion and counseling of risks of these approaches are of the utmost importance. Ideally, a multidisciplinary team of gynecologic oncologists, psychologists, reproductive-endocrinologists and maternal-fetal-medicine doctors will partake in the care of these women. Ongoing prospective protocols will hopefully clarify risks and benefits of conservative treatment in gynecologic cancers.

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