

## MINI-REVIEW

# Fertility Sparing Treatments in Young Patients with Gynecological Cancers: Iranian Experience and Literature Review

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### Abstract

With increase in the marriage age some women experience gynecological cancers before giving birth. Thus fertility sparing in these patients is an important point and much work has been done on conservative management. We here report our experience on fertility sparing with cervical, endometrial and ovarian cancers and include a review of the literature. With cervical cancer, radical trachelectomy with para-aortic and pelvic lymphadenectomy can be performed in patients with early stage IA1-IB cancers, because they have low recurrence rates. The complications are fewer than with radical hysterectomy. For endometrial cancer, the accepted treatment is total abdominal hysterectomy+ bilateral salpango-oophorectomy (TAH+BSO), but in young patients with early stage 1 lesions, we can suggest use of hormonal therapy in place of radical surgery if we evaluate with MRI and the result is early stage disease without the other site involvement and the grade of tumor is well differentiated. GnRH analog, oral medroxyprogesterone acetate (MPA), 100-800 mg/day, megestrol acetate 40-160 mg/day and combination of tamoxifen and a progestin have been applied, but we must remember, they should undergo repeated curettage for investigating medical outcome after 3 months. With normal pathology we follow medical therapy for 3 months and can evaluate for infertility treatment. The best option for patients who treated by medical therapy is TAH+BSO after normal term pregnancy. With ovarian cancer, there is much experience on fertility sparing surgery and in Iran conservative surgical management in young patients with stage I (grade 1,2) of epithelial ovarian tumor and sex cord-stromal tumor and patients with borderline and germ cell ovarian tumors is being successfully performed.

**Keywords:** Gynecological cancers -fertility sparing - complications - recurrence - outcome

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### Introduction

In 2005 there were an estimated 79,480 newly diagnosed cancer of female genital system in the US, approximately 28,910 women will die if these types of disease (Leitao and Chi, 2005). Today treatment of gynecologic cancer is possible through surgery, radiotherapy and chemotherapy which lead to high remission and long term survival rates. In these cured patients, quality of life is increasingly important meanwhile the ability to produce and raise normal children is considerable (Partridge, 2004). Nowadays delaying childbearing for social and financial reasons leads to more women suffering from fertility threats due to early-stage cancer being discovered (Maltaris, 2006). The patient may suffer from premature menopause and infertility which may impact her quality of life and self-

esteem significantly (Meirow, 1999). We are reporting our experience on fertility sparing in cervical, endometrial and ovarian cancers and the other experience in the literature.

### Cervical Cancer

Cervical cancer is a worldwide public health problem (Parkin et al., 1999). It is the most common gynecological cancer following breast cancer in almost always developing countries like Iran (Behtash, 2009; Karimi Zarchi et al., 2009). In 2005 in United States, 10,370 new cases were estimated and 3,710 deaths were occurred (National Cancer Institute, 2005). 42% of cervical cancer patients are younger than 45 years old, and about 30% of cervical cancer are diagnosed in women in their reproductive age (Nguyen et al., 2000) which they consider about their fertility and sexual problems (Lee et al., 2006).

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Definite treatment of stage IA2-Ib1 of cervical cancer is radical hysterectomy with total pelvic and Para aortic lymphadenectomy which is an effective therapy with low recurrence rate in early stages, but the main problem is infertility (Abu-Rustum et al., 2005; 2006). Pre-invasive lesions and some microinvasive carcinoma (stage IA1 without lymphovascular invasion) manage by procedures such conization, cryosurgery or loop electrosurgical excision procedure (LEEP). LEEP increase risk of preterm delivery and low birth weight infant (Samson, 2005) but it is an interesting option for women who consider future pregnancy (Paraskevaidis et al., 2002).

Semi-radical resection operation has been used in most solid tumors but partial resection of pelvic viscera as radical abdominal or vaginal operation are a new technique in gynecology oncology field. This technique is verified in women suffering from primary cervical cancer who wish to preserve their fertility (Dargent et al., 1994; Sonoda et al., 2004).

Radical trachelectomy is defined as removal of cervix and parametrium, preserving ovaries and uterus body and grafting uterus body to vagina at the end of the operation. In about 48% of women younger than 40, radical trachelectomy is a good option to preserve fertility (Chi, 2003). We can do two types of this procedures; radical abdominal trachelectomy and vaginal trachelectomy.

Radical vaginal trachelectomy (RVT): Dargent et.al originally reported this technique to preserve fertility which makes it possible to remove pelvic and Para-aortic lymph nodes and preserve fertility in early stages of cervical cancer. This technique had been spread between 1980 and 1990 which was a simpler technique than vaginal hysterectomy (Dargent et al., 1994; Sonoda et al., 2004) and used in patient with early cervical cancer (stage IA1, IA2, IB & IIA) (Dargent et al., 1994). the recurrence rate and the death rate are less than 5% (Silva-filho et al., 2007). In 2005, Klemm studied uterus body reserve following radical trachelectomy on 14 cases of primary cervical cancer and find by Doppler sonography that uterus perfusion after radical vaginal trachelectomy with bilateral pelvic and Para-aortic lymphadenectomy remained the same as healthy women (Klemm et al., 2005). 5-years survival of the patients with vaginal trachelectomy is 95% (Plante et al., 2004). Probability of bleeding from abdominal incisions may be more in vaginal trachelectomy, but other complications rate doesn't increase in abdominal approach comparable to vaginal one (Ungár et al., 2005). Although the rate of second trimester losses and preterm deliveries because of cervical weakness is high but the outcomes are satisfactory (Silva-filho et al., 2007)

Selection criteria for vaginal trachelectomy were as below: Age<45, fertility preservation, tumor size< 2cm, tumor stage: IA1 with lymphovascular invasion (conization indicated) or IA2 and IB1 without lymphovascular invasion, endocervix upper intact, lymph nodes involvement ruled out by paraclinic (Dargent et al., 1994; Silva-filho et al., 2007). Some believed it's better to perform radical abdominal hysterectomy in patients with tumor size>4cm and radical abdominal trachelectomy in one with tumor size 2-4 cm who wish to preserve

their fertility. Histology should be regarded in patients' selection for trachelectomy.

Radical abdominal trachelectomy with uterus body preservation was explained by Aburel et.al in 1981 (hat couldn't preserve fertility and was limited to cervical conization in primary stages of cervical cancer (Smith et al., 1997). This technique is proper in children whom vaginal manipulation is less possible (Abu-Rustum et al., 2005; 2006; Ungár et al., 2005) but in adult the aim is more removal of parametrium in comparison with vaginal technique. Compare to the RVT in this technique we have wider parametrial resection, lower complication rate and seems to be more familiar to gynecologic oncologists (Rodriguez et al., 2001)

In 2005, a retrospective review of 11 articles on radical trachelectomy was done by Boss et al. (2005) Of total 153 patients, 42% decided to become pregnant in whom 70% successful pregnancy occurred. Its complication is cervical narrowing that solved by dilatation of cervix. (Plante ,et al.,2005) Reported pregnancy outcome of 72 vaginal trachelectomy cases in 2005. First trimester abortion 16%, 2nd trimester abortion 4% and termination of pregnancy 4% was reported. Pregnancy outcome is acceptable in patients underwent trachelectomy.

Early detection of recurrent may impact survival of patient undergo radical trachelectomy (Bodurka-Beverset al., 2000). Close follow up is necessary in any patient diagnosed with and treated for invasive cervical cancer. Cytology evaluation of vaginal vault should be done every 3-4 month for 2 year, every 6 month until 5 years (Morris et al., 1996).

Research show that RVT doesn't has any side effect on fertility. In 200 cases of pregnancy after RVT 66% lead to neonate birth. Premature birth before 37th week happened in 27% of the cases. Abortion rate in first trimester was 16-20% like general population and second trimester abortion was 9.5% (Plante et al., 2005; Jolley et al., 2007). If the tumor volume is less than 500mm, tumor size is less than 2 cm and invasion depth of stroma is less than 2mm we can do ultraconservative operations include simple trachelectomy or extensive conization with knife. In this condition, loop conization with or without laparoscopic lymphadenectomy will be a suitable option. Naturally, large studies should be done to assess safety of operation, Oncologic outcome and pregnancy complications

Due to without enough experience on radical abdominal hysterectomy and the other surgical procedure, we think the alternative treatment for fertility preservation on cervical cancer will be better. Also Iran has worked on oocytes freezing and we had better consider young patients with cervical cancer for oocytes conservative procedure and then pregnancy with surrogate uterus.

## Endometrial Cancer

Endometrial carcinoma is the most common female pelvic malignancy in developing countries and account about 7300 death in USA annually (Morris et al., 1996). It usually occurs after menopause but it has been reported that 3-5% of patients are younger than 40 years old (Gallup, 1984; Hoskins et al., 2000). Most of these

female have a history of ovary dysfunctions, anovulation, obesity, nulliparity, hormonal disturbances and infertility (Silva-filho et al., 2007). They also have strong desire to keep their fertility. Fortunately endometrial carcinoma is well differentiated in younger patients and usually is in earlier stage with better prognosis (Gallup, 1984; Kim et al., 1997).

In Podrat et al. study (1985), 11% of them show positive response to treat. Complex atypical hyperplasia of endometrium is a precursor of endometrial adenocarcinoma (the most common histological type of endometrial cancer) which has 25% chances to progress into endometrial cancer. The standard treatment for endometrial carcinoma includes staging laparotomy, total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic washing and lymph node sampling and evaluation of peritoneum cytology (DiSaia et al 1997; Kahu et al., 2001). The supportive therapy such as radiotherapy is also employed for high risk patients to prevent the recurrence (Hoskins et al., 2000). Although the ultimate treatment especially in early stages is surgery, hormonal treatment has been suggested for women who anxious to conserve their fertility. In the last 30 years, a limited number of reports has suggested that young patient with Endometrial carcinoma may be treated conservatively with progestin to preserve fertility (Kistner et al., 1970; Kim et al., 1997). Successful treatment of severe and recurrence endometrial cancer with progestin agents could be done.

Saegusa found that cancerous cells contain progesterone receptors which respond well to the progesterone treatment and therefore they suggested that it is possible to keep the fertility in women with endometrium cancer (Saegusa et al., 1998). The average of the duration of their treatment was 5.4 months with 20 cases of pregnancy. 24% had recurrence after in average 19 months. No death was reported (Silva-filho et al., 2007). Prognostic factors at stages I-II are type of cells, grade of histology, depth of the myometrium invasion, peritoneal cytology, involvement of the lymphatic system, and age.

Guido and co-workers reported that apart from cases that cancer is presented as a polyp or limited to a small location in the endometrium, biopsy is efficient mode to evaluate the cancer (Larson et al., 1995). But D&C as the most effective method particularly use to determine the grade of the tumor (Ong et al., 1997) that in 60% of patient only less than 1/3 of the endometrium surface is evaluated (Stock, 1975). MRI, CTscan, and ultrasonography have been used to explore the invasion of the tumor to the myometrium or involvement of the cervix (Varpula, 1993), but among them MRI with contrast is sensitive and specific for detecting the myometrium invasion and reveal the involvement of the cervix (Zarbo et al., 2000). If it was inconclusive, laparoscopic exploration with peritoneal cytology, pelvic lymph node sampling and adnexa evaluation should be done (Benshushan et al., 2004)

Various doses of different progestational agents have been used in an effort to preserve fertility in young patient with clinical stage I Endometrial carcinoma (Silva-filho et al., 2007). Oral medroxyprogesterone acetate (MPA), 100-800 mg/day, megestrol acetate 40-160 mg/day and

combination of tamoxifen and a progestin have been used for treatment although they have similar results (Silva-filho et al., 2007). Endometrial biopsy and CA-125 and serial endovaginal US should be done for follow up (Kahu, 2001; Gotlieb et al., 2003)

## **Ovarian Cancer**

Ovarian cancer is the second most common gynecological cancer (Gonzalez-Lira et al., 1997). The incidence gradually rises with old age, with its peak near the seventh decade. In 2005 there were an estimated 22,220 new cases and 16210 deaths in USA (National Cancer Institute, 2005). 89% ovarian tumors occur after the age of 40 years and the reminders occur before of this age (Zanagnolo et al., 2005).

Standard treatment for borderline and malignant ovarian tumors is cytoreductive surgery as hysterectomy and oophorectomy, partial omentectomy and surgical staging. Surgical staging reveals the need of adjuvant chemotherapy to detect extension of the disease. Cytoreductive surgery will cause infertility and due to this problem, conservative surgery has been introduced (Amos et al., 2002; Jonathan et al., 2005).

Ovarian tumors contain 4 different tumors: Epithelial ovarian tumor (EOC) that has 90% survival of 5 years in patient with stage IA grade 1 (Morice et al., 2001, Seracchioli et al., 2001) and are diagnosed late mainly in stages III & IV (Gonzalez-Lira, 1997) that radical surgery plus chemotherapy is usually indicated for stage I disease. Conservative approach is indicated after a complete surgical staging (Silva-filho et al., 2007), Germ cell tumor (GCT) response of 80% of pre-adolescent malignant ovarian neoplasms; that diagnosed in 16-20 years old (Talamanca et al., 2002), Sex-cord stromal tumor (SCST) that have 85-100% survival of 5 years in stage IA, sertoli-lydig cell tumor response of 0.5% of all ovarian tumors (Young et al., 1984). Ovarian tumors that have been diagnosed in premenopausal period are mostly in early stage and lower grade and could be treated by conservative surgery (Ayhan et al., 2003). By many studies had showed that conservative surgery in patients with germ cell ovarian tumors is successful in outcome and preservation of fertility (Zanagnolo et al., 2004). Conservative surgery had been performed on patients with epithelial ovarian tumors in early stage even with adjuvant chemotherapy in stage Ic and grade 3 (Zanetta et al., 1997).

Conservative surgery could be performed on premenopausal patients with selective histological type of ovarian tumors, who desire to preserve fertility, even in higher stage or grade. But in epithelial ovarian tumors, it could be done just in early stages (up to stage Ic). (Ghaemmaghami et al., 2008). Unilateral salpingo-oophorectomy with preservation of the contra lateral ovary and the uterus now is considered the appropriate surgical treatment for patients with Stage IA grade 1 epithelial ovarian cancer, any stage borderline ovarian tumors with no invasive implants, SCSTs and MOCs (malignant ovarian germ cell tumors), even in the case of advanced germ cell disease, particularly if the contra lateral ovary is normal (Ghaemmaghami et al., 2008).

**Table 1. Comparison of Current Series and Other Studies of Epithelial Ovarian Tumors**

Authors	Years	P. no	Me an age	Histologic Type	Staging	Follow up	Recurrence	Preg.
Zanetta & et al (1996)(17)	10yr	99	-	-	Stage Ia	30 M	-	25(17)
Raspagliesi & etal (1997)(18)	1980-94	10	22.7yr	Ser(5) MUC(4) Undiff(1)	Stage Ia(2) (G3) Stage Ic(2) Stage III(2) Stage IIIc(4)	70 M	-	3
Morice & et al (2001)(19)	1982-99	25	24yr	Ser(16) MUC(19)	Stage Ia(19) GI=9 G2=10 Stage Ic=2 Stage II=2 Unknown=2	42 M	7	14
Morice & et al (2005)(20)	1987-2004	34	27 yr (14 - 36)	Muc (21) Ser(3) Endometrial (5) Small cell(2) Mixed(3)	Stage Ia(30) Gi=13, G3=3 Stage Ic=(3) Stage IIc(1)	60 M	10	10 (9)
Current series (2005)	2000-2004 (5yr)	10	26.2 (19 - 32)	Ser(5) Muc(4) Brenner(1)	Stage I(6) G1=3/2/1 Stage Ic(3) Stage IIIc(1)	30 M	2 serous stage Ic, stage IIIc	1

The detection of recurrence after fertility-sparing surgery can be done with ultrasound (US), physical examination and CA-125 which US is better (Benjamin I, et al, 1999). US can be done every 3 month for the first 2 years after surgery and every 6 month thereafter for recurrent (Zanetta et al., 2001).

## Conclusion

Fertility preservation options should be suggest for all young patients desiring future childbearing. If these methods don't work, the patient should be encouraged to consider a combination of several methods. There are no contraindications to combine IVF (in vitro fertilization) and embryo cryopreservation for a couple or unfertilized ova vitrification for the single young woman with GnRH analogue administration and in high risk cases also ovarian tissue cryopreservation (Gurgan et al., 2008) but embryo cryopreservation is inappropriate for children or unmarried women because this technique involve a male partner, unless sperm donation is acceptable (Paraskevaidis et al., 2002). There should be a gap between treatment and pregnancy because of recurrence danger and of course their next pregnancy are a high risk one (Blumenfeld et al., 2004). But long delay conception should be avoided

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