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Ovulatory failure, fertility preservation and reproductive strategies in the setting of gynecologic and non-gynecologic malignancies

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Summary

The advances in assisted reproductive technology over time have paralleled the insights gained into the natural history of different gynecologic malignancies. Subgroups of young patients with early stage ovarian cancer, endometrial carcinoma and cervical carcinoma may be considered to be at relatively low risk of recurrence and may be treated conservatively with the aim to preserve fertility when this is of prime concern. Unilateral adnexectomy with preservation of the contralateral ovary and uterus may be appropriate for some patients with epithelial ovarian cancers, and certainly should be the procedure of choice for those young women with borderline tumors and early stage sex cord-stromal and malignant germ cell tumors. Administration of high-dose progestins may obviate the need for immediate hysterectomy in a young patient with a well-differentiated endometrial carcinoma desirous of childbearing. The performance of vaginal radical trachelectomy in conjunction with laparoscopic pelvic lymphadenectomies has emerged as a real breakthrough for a highly select group of young women with early invasive tumors of the cervix. In this review, we also discuss reproductive strategies for women who experience chemotherapy-induced ovulatory failure and also address the potential for ovarian cortex cryopreservation and transplantation, and uterine transplantation, all of which are looming on the horizon.

Key words: Fertility preservation; Malignancy; Conservative surgery; Infertility.

Ovulatory failure and reproductive strategies

Infertility and fertility drugs

Primary infertility is an established risk factor for the subsequent development of epithelial ovarian cancer. The hypothesis which has been advanced to account for this observation is one in which incessant ovulation (i.e., uninterrupted by pregnancy and lactation) results in the opportunity for errors in DNA synthesis to occur when the ruptured surface epithelium of the female gonad is reconstituted. Although DNA mismatch-repair gene products function as tumor suppressor proteins to prevent the propagation of such nucleotide errors, the more ovulatory cycles that occur increase the probability of erroneous repair. It is interesting that a certain Long Island chicken breed exhibits unilateral ovulation throughout life and only develops ovarian carcinoma from the ovulatory side [1]. Further support for the 'incessant ovulation theory' comes from the established reduction in risk for the development of ovarian cancer afforded by the prolonged use of ovulation-inhibiting oral contraceptive use [2].

In 1992, Whittimore *et al.* collected data from 2,197 white ovarian cancer patients and 8,893 white controls in 12 United States case-control studies conducted from 1956 through 1986 [3]. Clear trends of decreasing risk for ovarian cancer were evident with increasing number of pregnancies and increasing duration of breast feeding and oral contraceptive use. The risk was increased among women who had used fertility drugs and among women with long total duration of premenopausal sexual activity without birth control; these associations were particularly strong among the nulligravid. Their observations suggested that pregnancy, breast feeding, and oral contraceptive use induce biological changes that protect against ovarian malignancy. The investigators suggested that a small fraction of the excess ovarian cancer risk among nulliparous women is due to infertility, and that any increased risk associated with infertility may be due to the use of fertility drugs.

During that same year, Harris *et al.* (from Whittimore's group) combined data from nine case-control studies, conducted from 1974 to 1986, representing 327 white women with ovarian tumors of low malignant potential and 4,144 white controls [4]. The risk profile for tumors of low malignant potential was found to be similar to that for invasive tumors, with two exceptions. Compared with that of invasive tumors, the risk of borderline tumors was less clearly reduced among women who had used oral contraceptives and more clearly elevated among women with a history of infertility.

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Recently, Ness *et al.* pooled interview data on infertility and fertility drug use from eight case-control studies conducted between 1989 and 1999 in the United States, Denmark, Canada, and Australia [5]. Included in the analysis were 5,207 cases and 7,705 controls. Among nulligravid women, attempts for more than five years to become pregnant compared with attempts for less than one year increased the risk of ovarian cancer 2.67-fold (95% confidence interval (CI): 1.91, 3.74). Fertility drug use in nulligravid women was associated with borderline serous tumors (OR = 2.43, 95% CI: 1.01, 5.88) but not with any invasive histologic subtypes. Their data suggest a role for specific biologic causes of infertility, but not for fertility drugs in overall risk for ovarian cancer. Parenthetically, Tewari and co-workers have reported an immature teratoma arising during pregnancy in a 37-year-old following ovarian hyperstimulation [6]. Malignant germ cell tumors are rarely discovered in women over 30 years, but because ovarian hyperstimulation recruits oocytes (which are also derived from germ cells), if there is a link between fertility drug therapy and ovarian cancer, a germ cell malignancy would not be unexpected.

Effects of chemotherapy on fertility

The adverse effects of chemotherapy on dividing germ cells were first recognized in 1948 when Spitz reported the histological effects of nitrogen mustards on human tissues and tumors [7]. Most of the reports in the literature focusing on gonadal toxicity after chemotherapy have concerned patients treated for leukemia, testicular and prostate cancer, and breast cancer. In addition, fertility problems, including male azoospermia and female amenorrhea have been documented following treatment for lymphoma. Azoospermia can develop in up to 60% of patients and oligospermia in 30% following high-dose cyclophosphamide therapy [8]. Similarly, 35% to 90% of women may experience menstrual irregularities or sustained ovarian failure following chemotherapy for breast cancer, soft tissue sarcomas, and lymphoma. Patients undergoing chemotherapy for gestational trophoblastic disease, testicular tumors, Hodgkin's disease, acute lymphoblastic leukemia, and other tumors are now expected to survive for prolonged periods, and the majority are cured. Most of these patients are of reproductive age, and some are in the prepubertal period.

Amenorrhea

The likelihood of chemotherapy-induced amenorrhea is based on the specific chemotherapy regimen administered and the age of the patient. Reports indicate a high incidence of amenorrhea and oligomenorrhea in previously menstruating women treated with alkylating agents [9]. Ovarian pathologic findings seem to be fairly uniform. There is a depression in follicular maturation without primordial follicle development. Ovarian fibrosis may result with a total lack of follicles on histologic examination.

The severity of follicular depletion is a function of the number of oocytes available for maturation and the activity of follicles present at the initiation of chemotherapy, with pre-ovulatory follicles being most sensitive. Quiescent prepubertal ovaries not yet under cyclic hormonal control seem protected against destruction from chemotherapy. Prepubertal girls show almost uniformly normal development of menses after alkylating agent chemotherapy, but postpubertal patients show variable responses. Schilsky *et al.* reported a study of breast carcinoma patients receiving adjuvant chemotherapy with melphalan or melphalan plus 5-fluorouracil [10]. Amenorrhea occurred in 22% of the patients younger than 39 years and in 73% of the patients 40 years or older. The effects of chemotherapy are not only age-dependent, but also dose-dependent, with damage occurring to many follicles during prolonged treatment.

Franchi-Rezgui *et al.* identified 84 women under 40 years at diagnosis of lymphoma who were treated with three or more chemotherapy cycles including alkylating agents [11]. None of the patients received pelvic or total body irradiation. With a median follow-up of 100 months, 31 women became pregnant, 34 experienced premature ovarian failure, and 19 women retained relative fertility. Those patients with ovarian failure were older at diagnosis than those women with preserved or relative fertility (30.6 years vs 24.3 years), had a higher relapse rate, and received high-dose therapy (i.e., cyclophosphamide, etoposide, and BCNU) more frequently. Following high-dose therapy (n = 26), only three women (ages 25-27 years) became pregnant.

Gershenson described 40 patients treated with multiagent chemotherapy for malignant germ cell tumors of the ovary [12]. The median age at onset of therapy was 15 years. Twenty-eight patients who received vincristine, doxorubicin, and cyclophosphamide (VAC) chemotherapy have resumed regular menses; only three of the remaining patients have had serious menstrual irregularities. The final outcome appears to be related to age: the younger the patient, the larger the reserve of oocytes that can be recruited after chemotherapy to re-establish the normal ovulatory state. *Return of menses and ovulation is therefore a function of age.*

Ovarian tissue banking

Although sperm banking is commonly performed, female gametes are not so amenable to cryopreservation with poor pregnancy rates reported when frozen-thawed unfertilized oocytes are utilized. An option for patients scheduled to receive chemotherapy is to postpone cancer treatment to enable ovulation induction and oocyte aspiration. Whenever possible, the retrieved oocytes should be fertilized in vitro prior to cryopreservation, with donor sperm offered to single patients. These frozen embryos could then be used to produce pregnancies if chemotherapy-related ovarian failure occurs.

In the 1950s, laboratory research on *ovarian cortex cryopreservation and transplantation* commenced [13]. Clinical studies were undertaken in the 2000s. Although cryopreserved ovarian tissue has the potential to restore ovulatory function in women who experience premature ovarian failure as a consequence of chemotherapy, no pregnancies have been reported to date and the technology remains investigational [14]. Better cytoprotectants and improved cryopreservation techniques are necessary, along with a further understanding of the process of revascularization.

Radiotoxicity

When extra-pelvic radiotherapy is required during pregnancy to treat brain tumors, breast cancer and some cases of Hodgkin's disease, fetal dose estimates can be made from in vivo and phantom measurements using thermoluminescence (TL) dosimeters and an ionization chamber. These data can then be extrapolated to estimate the radiation scatter to the ovaries in scenarios where the mother is expected to survive and preserved ovulatory function is important. In vivo measurements are performed by inserting a catheter with TL dosimeters or an ionization chamber into the patient's rectum. Phantom measurements are performed by simulating the treatment conditions on an anthropomorphic phantom. In the non-pregnant patient being treated with pelvic irradiation, oophoropexy or lateral ovarian transposition is an option to preserve ovulatory function.

Oophoropexy in Hodgkin's disease

Total lymph node irradiation (TNI) for Hodgkin's disease typically delivers a dose of 2000-4000 cGy to the ovaries, which invariably results in premature ovarian failure and infertility unless the ovaries are shielded. Transposition of the ovaries away from the pelvic nodes at staging laparotomy has had mixed success. In addition, some ovaries migrate back to their original positions. Le Floch *et al.* reported in 1976 their results in young female patients irradiated for Hodgkin's disease who had undergone oophorexy behind the uterus at the time of surgical staging [15]. When pelvic irradiation was administered, a 10-cm thick lead block was used to shield the ovaries in the midline. The minimum radiation dose to the ovaries was 350 to 400 cGy over 39 days to 46 days. Two-thirds of their patients retained ovarian function, and nine who received high-dose pelvic irradiation conceived. Six patients gave birth to eight babies. Two patients have had therapeutic abortions, and one experienced a spontaneous abortion. No abnormalities have been observed in the children. In contrast, Hunter *et al.* described 46 patients who underwent oophoropexy for Hodgkin's disease, and found that among 12 patients who were treated with irradiation alone, including the inverted Y field, only one patient maintained normal ovarian function [16]. Williams *et al.* have described a laparoscopic technique that allows transposition of the ovaries just prior to pelvic radiation [17]. The procedure was carried out in 12 patients, five of whom had evidence of ovarian function at follow-up. Among these five women, the number of courses of chemotherapy ranged from zero to two courses. Four of these patients have achieved pregnancies. Two patients of the original cohort have died, and of the five patients with ovarian failure at follow-up, four had received multiple courses of chemotherapy. Because of recent changes in therapy favoring systemic chemotherapy rather than total nodal irradiation for patients with Stage III Hodgkin's disease, the need for oophorpexy may be less than previously described, but the effects of chemotherapy on ovarian function will remain a central issue in young female patients.

Reproductive function following therapy for Hodgkin's disease

A report by Holmes and Holmes addresses the reproductive prospects for patients with Hodgkin's disease after therapy [18]. Their study compared the outcome of 93 pregnancies in 48 patients with 228 pregnancies in 69 sibling controls. No statistically significant differences for spontaneous abortions or abnormal offspring were noted when all patients were compared with all control subjects or when 35 irradiated patients were compared with all control subjects. The pregnancy outcome of 13 patients who received both irradiation and chemotherapy before pregnancy appeared to be compromised compared with the control subjects. Wives of male patients in this category were more likely to have spontaneous abortions than were wives of control men; female patients in this category were significantly more likely to produce abnormal offspring than were control women. Thus, in this series of patients, therapeutic irradiation alone did not appear to jeopardize post-treatment reproduction in fertile patients with Hodgkin's disease. However, in the smaller group of patients who received both irradiation and chemotherapy, the reproduction picture was statistically not as good. Horning and colleagues reported on the probability of maintaining ovarian function after successful therapy for Hodgkin's disease (Figure 1), illustrating the importance of age at treatment [19].

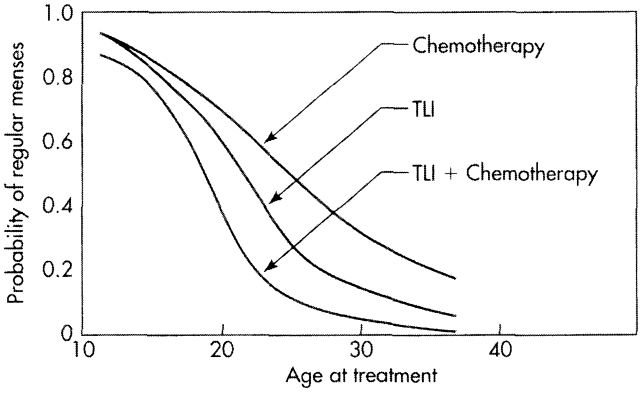


Figure 1. — Reproductive potential after Hodgkin's disease. TLI – total lymphoid irradiation. Modified from: Horning S.J. *et al.* Female reproductive potential after treatment for Hodgkin's disease. *NEJM*, 1981, *304*, 1377 (used with permission).

Fertility preservation in the setting of gynecologic malignancy

Twenty-one percent of gynecologic cancers occur among women in the reproductive age group who are yet to complete or commence a family. For many, the idea of losing their uterus and/or their ovaries to treat their cancer is devastating. Although patients can be offered alternative reproductive options, such as *in vitro* fertilization (IVF) with embryo cryopreservation and gestational surrogacy, those approaches remain fairly complex and are not ethically acceptable or affordable to many [20]. The question whether some lesions can be addressed in a conservative surgical manner has gained considerable attention during the preceding decade. Through randomized chemotherapy and surgery trials, and improvements in molecular pathology, low risk groups of patients have been identified among those afflicted with gynecologic malignancy. Select patients within these groups may be candidates for conservative surgery and/or a fertility-sparing approach; in other instances, the implementation of assisted reproductive technologies have been of considerable value.

Ovarian cancer

While greater than two-thirds of patients with ovarian cancer present with metasatic disease, FIGO Stage I borderline and invasive tumors are more frequent in women of childbearing age, with malignant germ cell tumors being diagnosed exclusively in young women. Among patients with FIGO Stage I epithelial lesions, an evaluation of tumor grade, ploidy state, histologic subtypes, FIGO substage and serum CA125 measurements can assist in identifying those patients who may be treated conservatively. The majority of malignant germ cell tumors are exquisitely chemosensitive and a conservative surgical approach may be entertained even for some patients who present with disseminated disease.

Malignant germ cell tumors

Because malignant germ cell tumors of the ovary have been rendered nearly 90% to 95% curable with the use of postoperative systemic therapy, it is not surprising that much of the available literature on fertility-sparing surgery has focused on young women who harbor such lesions [21]. For example, in the study cited earlier by Gershenson *et al.*, of the 16 patients attempting pregnancy following conservative surgery and chemotherapy, 11 delivered 22 healthy infants [12]. Low *et al.* undertook a retrospective review of 74 patients with malignant germ cell ovarian cancers treated by conservative surgery (i.e., unilateral adnexectomy with preservation of the contralateral ovary and uterus) [22]. Chemotherapy was given to 63.5% of the study group. Survival for patients with Stage I disease was 98.2% and that for patients with advanced disease stages was 94.4%. During chemotherapy 61.7% of patients developed amenorrhea but 91.5% of these women resumed normal menstrual function on completion of chemotherapy. Fourteen healthy live births were recorded in the chemotherapy group and there were no documented birth defects. There was one case of infertility (1.4%).

Zanetta *et al.* collected 169 cases of women with malignant germ cell ovarian tumors seen between 1982 and 1996 [23]. Fertility-sparing surgery was performed in 138 women (81%), 81 of whom received postoperative chemotherapy. For women who were treated conservatively, the survival rate ranged from 90% to 100%, depending on the cell-type. After treatment, all but one postpubertal woman had recovery of menses within nine months. During follow-up, 12 untreated and 20 treated patients had 55 conceptions. The investigators recorded 40 pregnancies at term, six terminations, and nine miscarriages. Four malformations were observed: one in 14 conceptions of patients who had not received chemotherapy and three in 41 conceptions of treated patients. The investigators concluded that irrespective of subtype and stage, conservative surgery should become the standard approach to treating most patients with malignant ovarian germ cell tumors. Additionally, fertility appeared to be only marginally affected by treatments, with miscarriages in the expected range for the general population. Although the malformation rate was slightly higher than in the general population, no significant difference was seen between patients who did and did not receive systemic chemotherapy.

Tangir *et al.* have noted that fertility-preserving surgery followed by chemotherapy is effective in conserving reproductive function, even in women with advanced stage germ cell tumors [24]. They included 86 women with malignant germ cell tumors in their 2003 report. Fertility-preserving surgery was performed in 64 patients. Thirty-eight attempted conception and 29 have achieved at least one pregnancy (76%). Among the patients who conceived, 20 had FIGO Stage I tumors, one was FIGO Stage II, and eight were FIGO Stage III. Sixteen of these patients had received vincristine, actinomycin D, and cyclophosphamide; three received cisplatin, vinblastine, and bleomycin; three received bleomycin, etoposide, and cisplatin; one received etoposide and cisplatin; two were treated with other combinations; and four did not receive any chemotherapy. Among the nine patients who could not conceive, seven had FIGO Stage I tumors, and two were FIGO Stage III. Four of these nine patients received vincristine, actinomycin D, and cyclophosphamide; three received etoposide and cisplatin; one received cisplatin, vinblastine, and bleomycin; and one patient received no chemotherapy. A total of 38 children were born to these women, and for 16 children with available follow-up, there has been no evidence of congenital or developmental anomalies.

Borderline tumors

Survivorship for patients with borderline ovarian tumors is also high. Because only a small proportion of cells from an ovarian neoplasm of low malignant potential are in the actively dividing pool, postoperative systemic chemotherapy (which is often cell-cycle specific) is not useful. French investigators offered conservative surgery to 44 women with Stage I-III borderline ovarian tumors, 33 of whom underwent unilateral adnexectomy and 11 who had undergone cystectomy. Seventeen pregnancies (of which 15 were spontaneous) occurred in 14 patients; 13 pregnancies occurred in patients with Stage I disease and four occurred in patients with Stage III disease [25].

Camatte *et al.* assessed the fertility of women treated conservatively for Stage II (n = 6) or III (n = 11) serous borderline ovarian tumors [26]. Eight pregnancies were observed in seven patients at a median delay of eight months following the surgical procedure. Six pregnancies were observed spontaneously, one occurred after an ovarian stimulation and one after an in vitro fertilization (IVF) procedure. None of these patients recurred under the form of invasive ovarian carcinoma on the spared ovary. The investigators suggested that spontaneous pregnancy can occur after conservative treatment of advanced stage borderline tumors of the ovary with non-invasive implants without affecting overall survival.

Beiner *et al.* evaluated 43 patients who underwent conservative management of borderline ovarian tumors, nine of whom developed a local recurrence [27]. Nineteen women delivered a total of 25 healthy children, seven of whom required IVF. Four of these patients developed recurrent disease prior to (n = 2) and after (n = 2) IVF, all of whom were rendered disease-free with up to 26 months follow-up. Chan *et al.* studied 25 women with borderline ovarian cancers managed with preservation of the uterus and at least a portion of one ovary. The median age was 29 years and the stage distribution included 10 with Stage IA, three with Stage IC, one with Stage IIIA, and 11 with unstaged disease. There were no recurrences during a median follow-up of 80 months (range, 4-157 months). Among six women who attempted to become pregnant, five succeeded, resulting in a total of five live births [28]. In contrast to the experience reported by Chan *et al.*, Donnez *et al.* documented an 18.7% recurrence rate among 16 patients treated conservatively for borderline tumors of the ovary, although there were no deaths due to disease. Among 11 women who attempted pregnancy, 12 pregnancies were reported in seven [29]. Finally, Seracchioli *et al.* reported on laparoscopic management of borderline ovarian tumors in 19 patients, one of whom recurred and was re-treated laparoscopically [30]. Six of ten patients who attempted pregnancy, conceived at a mean follow-up of 42 months and went on to deliver healthy babies at term.

Invasive ovarian carcinoma

The literature concerning conservative surgical management of frankly invasive epithelial carcinomas is sparse. Based on the available information, Williams advises that any ovarian enlargements be promptly and adequately evaluated [31]. Traditionally, a lesion of high grade or high stage has not been regarded as being amenable to conservative surgery, and definitive total abdominal hysterectomy, bilateral salpingo-oophorectomy with or without partial omentectomy, lymphadenectomy, peritoneal biopsies, and subsequent chemotherapy has been the rule. Certainly, in the setting of a high grade lesion, if the uterus and contralateral ovary appear normal and the woman is desirous of childbearing, a consideration can be made to leave those organs in situ and continue treatment with chemotherapy.

In the individual who has a low-grade and intracystic or encapsulated ovarian neoplasm, conservative surgery may be considered, provided there is no evidence otherwise of any peritoneal or other spread. The performance of a wedge resection of the contralateral ovary to obtain histologic certainty that it is devoid of neoplasia may be considered, but this may result in mechanical sterility and should not be performed in a grossly normal-appearing ovary. When the diagnosis is in doubt based on intraoperative rapid mandatory frozen section analysis (especially in those cases involving clinical Stage I tumors), we prefer a two-stage approach, and defer definitive surgery to a later date (if needed) once the final pathology has been made available. If on final review, an ovarian preserving operation is selected in the setting of invasive carcinoma, it would also seem preferable to complete the surgical procedure with hysterectomy and salpingo-oophorectomy at a future date once the patient's family is complete, thus obviating any possible appearance of a malignant tumor in the remaining ovary. In the setting of bilateral ovarian carcinomas, conservative surgery is indefensible.

Morice *et al.* evaluated clinical outcome and fertility in 25 patients treated conservatively for epithelial ovarian carcinoma [32]. The FIGO stage distribution included 19 with FIGO Stage IA (grade 1, n = 9; grade 2, n = 10), one with FIGO Stage IC, two with FIGO Stage II, and three patients whose initial stage was unknown. Seven patients experienced recurrent disease, five on the remaining ovary. The disease-free survival rate at five years for the 19 patients with FIGO Stage IA tumors was 89% (grade 1) and 71% (grade 2). All patients with FIGO Stage IC or higher disease experienced recurrence. Only four pregnancies (three spontaneous and one after an IVF procedure) were obtained. The authors recommended that conservative surgery for patients with epithelial ovarian cancer be considered only in young patients with FIGO Stage IA disease who are adequately staged and desire to preserve fertility potential. They explicitly stated that conservative surgery should not performed in patients with disease staged higher than FIGO Stage IA.

Colombo's team analyzed the outcomes of 99 women under the age of 40 with Stage I ovarian carcinoma, 56 of whom were treated by conservative surgery (36 FIGO Stage IA, one with FIGO Stage IB, and 19 with FIGO Stage IC)

[33]. Relapse occurred in three patients with FIGO Stage IA (one patient each with grade 1, 2 and 3), but only one occurrence was in the residual ovary and the patient was rescued by surgery. The other two patients who relapsed at distant sites died as a result of their tumors. Seventeen patients who desired to become pregnant did so for a total of 25 conceptions. Their data support the possibility of some extension of the conservative approach as outlined above by Morice *et al.* [32, 34].

Experiences concerning the fertility outcomes of women treated with conservative surgery followed by systemic chemotherapy for ovarian carcinoma have also been reported. Two patients reported by Yoshinaka *et al.* with a clinical Stage IA mucinous adenocarcinoma (one of which was of borderline malignancy) underwent unilateral salpingo-oophorectomy and wedge resection of the ovary followed by cyclophosphamide, doxorubicin plus cisplatin or cyclophosphamide plus cisplatin, and at two and four years of follow-up have each delivered a healthy neonate at term [35]. Seidin *et al.* performed conservative (i.e., fertility-preserving) tumor debulking in a patient with a borderline tumor harboring invasive implants, who, following treatment with carboplatin, paclitaxel plus high-dose chemotherapy with peripheral blood stem cell rescue, went on to successfully conceive and deliver a healthy baby at term [33]. Schilder *et al.* reported on 52 patients with Stage I epithelial ovarian cancer treated from 1965 to 2000 [34]. Forty-two patients had FIGO Stage IA disease, and ten had FIGO Stage IC cancers. Twenty patients received adjuvant chemotherapy with regimens that included cisplatin, paclitaxel, carboplatin, melphalan, and cyclophosphamide. The duration of follow-up ranged from six to 426 months (median, 68 months). Five patients developed tumor recurrence eight to 78 months after initial surgery, three in the contralateral ovary. At the time of their publication in 2002, 50 patients were alive without evidence of disease, and two had died of disease. The estimated survival was 98% at five years, and 93% at ten years. Twenty-four patients attempted pregnancy and 17 (71%) conceived. These 17 patients had 26 term deliveries without congential anomalies, and five had spontaneous abortions. A summary by Schilder *et al.* of reported cases of Stage I epithelial ovarian cancer treated by unilateral oophorectomy is shown in Table 1 [23, 32, 37, 38]. One hundred and thirty-five out of 144 patients (94%) are alive with no evidence of disease at a median of 70 months after therapy. Forty-six women conceived, and were delivered of 54 term pregnancies. No congenital anomalies were reported in any of these pregnancies.

Ovarian hyperstimulation with oocyte retrieval

Because of the assisted reproductive technologies readily available, hyperstimulation of the unaffected ovary for oocyte retrieval in cases of unilateral ovarian cancer treated conservatively may be feasible [39]. This approach was reported by Fasouliotis *et al.* in five infertile women who underwent IVF procedures at a mean of 42.2 months following conservative surgery for borderline ovarian tumors [40]. Six pregnancies were achieved in three patients, with a pregnancy rate per retrieval of 37.5% and per transfer of 42.9%. Gallot *et al.* treated a FIGO Stage IIIA borderline serous tumor of the ovary conservatively in an attempt to preserve the fertility of a 21-year-old nulligravid patient [41]. Six months later, recurrent lesions were resected, and an 'urgent' IVF was performed to obtain frozen embryos. Oncological treatment was then completed by radical surgery with uterine conservation. Fifteen months later, two thawed embryos were successfully transferred and the patient delivered one baby. Pouly *et al.* discovered a clinical Stage IC serous epithelial carcinoma in a woman undergoing a diagnostic laparoscopy for an infertility investigation [42]. An immediate in vitro fertilization was scheduled to obtain frozen embryos. Oncological treatment was then completed by radical surgery (with uterine conservation) and chemotherapy. Two years later, the thawed embryos were transferred. The patient subsequently delivered two babies.

In surgically unstaged patients who have undergone unilateral adnexectomy for a clinical Stage I ovarian cancer, there have been reports of ovarian hyperstimulation and oocyte retrieval prior to comprehensive surgical staging with subsequent ex vivo fertililzation and frozen-thawed embryo transfer to a suitable surrogate uterus. Bernardini and Asch from Genova undertook a mandatory oncological consultation of a 25-year-old woman with Stage I ovarian cancer

Table 1. — *Fertility-sparing surgery in patients with Stage I epithelial ovarian cancer.*

Author	Year	Substage	N	Recurrence (N)	Site of recurrence	Survival	Median follow-up	Reproductive outcome (mos)
Zanetta *et al.* [20]	1997	IA IB IC	36 1 19	4 0 1	Brain, contralateral ovary, lung, spleen (n = 1 ea.) n/a Contralateral ovary	NED (n = 53), DOD (n = 3)	94 (34-175)	17 term deliveries (n = 20 patients)
Brown *et al.* [34]	2000	IA IC	12 4	2 0	Contralateral ovary n/a	NED (n = 14), DOD (n = 2)	66 (1-174)	8 term deliveries (n = 5 patients)
Morice *et al.* [29]	2001	IA IC	19 1	3 1	Contralateral ovary Not stated	NED (n = 18), DOD (n = 2)	47 (6-201)	3 term deliveries (n = 4 patients)
Schilder *et al.* [35]	2002	IA IC	42 10	4 0	Contralateral ovary (n = 3); lung, peritoneum (n = 1 ea) n/a	NED (n = 50), DOD (n = 2)	78 (3-423)	26 term deliveries (n = 17 patients)

NED: no evidence of disease; DOD: died of disease.

Adapted and updated from: Schilder *et al.* Outcome of reproductive age women with Stage IA or IC invasive epithelial ovarian cancer treated with fertility-sparing therapy. *Gynecol. Oncol.*, 2002, *87*, 1.

[43]. Her 30 year old fertile sister was participating in a program of IVF gestational surrogacy and the donor was recommended to prospectively undergo controlled ovarian hyperstimulation cycles for embryo banking before being treated by comprehensive surgery. Available embryos were cryopreserved and after adequate endometrial preparation using artificial cycles of hormone replacement therapy, three thawed frozen embryos were transferred to the surrogate. Unfortunately this pregnancy resulted in spontaneous abortion.

Endometrial cancer

While a large proportion of endometrial cancers express estrogen and progesterone receptors, recurrent tumors and metastases rarely express functional progesterone receptors. This may account for the limited response rates of 20% to 40% that are observed when palliative progestin therapy is used in the setting of advanced disease. At the other end of the spectrum, there have been several small series and case reports detailing the successful management of young women treated conservatively with progestin therapy for well-differentiated endometrioid adenocarcinomas (Figure 2) [44-56]. It should be recognized that one of the major difficulties in the interpretation of the results of conservative management in young patients remains the distinction between atypical hyperplasia and invasive carcinoma. Most of the reports published from 1968 to 2003 have not been associated with a rigorous pathology review (Table 2).

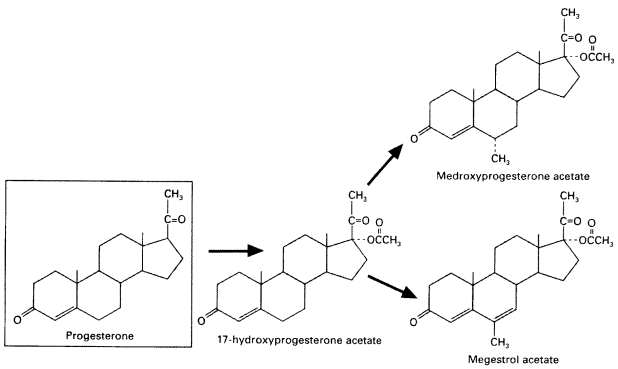


Figure 2. — Chemical structure of progesterone, medroxyprogesterone acetate, and megastrol acetate.

In all patients opting for conservative treatment, we recommend a thorough fractional dilatation and curettage to exclude worrisome features such as higher architectural grade virulent cell-types, and endocervical canal involvement. MR imaging of the uterus can be used to exclude deep myometrial invasion in some cases, and a chest radiograph is also advisable. Megastrol acetate is typically administered orally at a dose of 160 mg/day. Repeat endometrial sampling should be performed following three months of therapy to ascertain histologic improvement. Although the progesterone-releasing intrauterine device has been used successfully to treat clinical Stage IA endometrial cancer in patients at high surgical risk [54], its use has not been reported among patients seeking conservative therapy to preserve fertility.

One further point that should be emphasized is that endometrial cancer in young women has been linked not only to obesity but also to polycystic ovarian disease, primary or secondary infertility may coexist with the cancer in some cases, requiring assisted reproductive technology such as IVF or even intracytoplasmic sperm injection with embryo transfer [54-56].

Table 2. — *Summary of case series with > 5 patients treated with progestins for endometrial cancer.*

Author	Year	N	Mean age (yrs)	Initial response	Minimal time to response (mos)	Mean duration of treatment (mos)	Mean follow-up of responders (mos)	Outcome of responders	Fertility
Bokhman *et al.* [47]	1985	15	28	12/15	3	3.6	36-108	NED (n = 12)	ns
Kim *et al.* [43]	1997	7	32.4	4/7	3	3	12.9	Recurrence (n = 2)	ns
Randall *et al.* [48]	1997	12	30.5	9/12	3	9	35	Recurrence (n = 2)	5 deliveries
Duska *et al.* [49]	2001	12	31	ns	ns	ns	ns	Recurrence (n = 3)	5 deliveries
Wang *et al.* [41]	2002	9	32	8/9	2	ns	69	Recurrence (n = 4)	2 deliveries
Gotlieb *et al.* [42]	2003	13	31	13/13	3	3.5	78	Recurrence (n = 6)	7 deliveries
Total		68	30.8	46/56	2.8	4.8	–	–	19 children

NED: no evidence of disease; DOD: died of disease.
Adapted and updated from: Walter *et al.* Outcome of fertility-sparing treatment with progestins in young patients with endometrial cancer. *Obstet. Gynecol.*, 2003, *102*, 718.

Progestin therapy

Wang *et al.* treated nine women with clinical Stage IA, grade 1 endometrioid adenocarcinoma with hormonal therapy from 1991 to 1999 [44]. The median age of the patients was 32 years (range, 30-39 years). Of the nine patients, eight (88.9%) achieved complete remission after hormone therapy and four patients conceived (two patients had three term pregnancies and underwent consolidation hysterectomy after completion of family planning). Only one patient underwent hysterectomy for failure to respond; her tumor was estrogen-receptor and progesterone-receptor positive by immunostaining but negative by the ligand-binding method. Importantly, four responders later developed recurrent endometrial carcinoma. One underwent immediate hysterectomy. Two were successfully retreated with hormone therapy, but the other did not respond and underwent hysterectomy. All nine patients have been alive without evidence of disease 25 months to 113 months (median, 69 months) months from initial diagnosis.

Gotlieb *et al.* identified 13 patients who underwent conservative management with progestins and were followed for a mean of 82 months [45]. All patients responded to treatment within a mean period of 3.5 months, with normal pathology on follow-up endometrial samplings. Six patients suffered a recurrence at a median of 40 months. Four of these patients had a histologic complete response following a second course of progestins. At the time of publication in 2003, nine healthy infants had been born to three of the patients.

Kim *et al.* collected seven premenopausal women from their institution and 14 additional patients from the literature who were treated with progestin alone for well-differentiated endometrioid adenocarcinoma of the uterus [46]. Combining the data for all patients, 13 of 21 patients (62%) had an initial response to progestins. Three initial responders later developed recurrent disease, one of whom was found to have extrauterine disease at laparotomy. Eight of 21 patients (38%) did not respond to progestins and underwent more definitive treatment. None of these patients later developed recurrent disease. Six viable infants were delivered of three patients after therapy. Nineteen of 21 patients were alive without evidence of disease at last follow-up. The authors concluded that premenopausal women with endometrial carcinoma may be treated successfully with progestin therapy alone as primary therapy to preserve childbearing potential.

Uterine transplantation

Can assisted reproductive technology be of any value to the woman with a more advanced endometrial cancer for which hysterectomy is advisable (eg., clinical Stage I but of higher order architectural grade)? Because most endometrial cancers do not involve the ovaries, the potential for oocyte retrieval, *ex vivo* fertilization and embryo transfer to either a surrogate uterus or even to the cancer patient who has undergone successful progestin therapy or even uterine transplantation after hysterectomy may become possible.

The first successful technique of uterine transplantation was reported in 1966 using dogs [58]. The vessels around the uterus and ovaries were isolated, divided, and then reanastomosed with subsequent uterine function, including pregnancy. A group from the University of California, San Diego, have recently reported their techniques and successes performing orthotopic utero-ovarian transplants in rats [59]. Briefly, the utero-ovarian block is dissected out with the entire pelvic circulation intact, which is then anastomosed to the infrarenal aorta and inferior vena cava of the recipient.

In 2000, Fageeh *et al.* reported on the transplantation of the human uterus to a 26-year-old who lost her uterus six years earlier due to post-partum hemorrhage [60]. The donor, a 46-year-old patient with multiloculated ovarian cysts, underwent a hysterectomy modified to preserve tissue and vascular integrity. The donor uterus was connected in the orthotopic position to the recipient's vaginal vault and additional fixation was achieved by shortening the uterosacral ligament. The uterine arteries and veins were extended using reversed segments of the great saphenous vein, then connected to the external iliac arteries and veins, respectively. Immunosuppression was maintained by oral cyclosporine A (4 mg/kg body wt), azathioprine (1 mg/kg body wt) and prednisolone (0.2 mg/kg body wt). Allograft rejection was monitored by Echo-Doppler studies, MR, and measurement of the CD4/CD8 ratio in peripheral blood by fluorescence activated cell sorter (FACS scan). An episode of acute rejection was treated and controlled on the ninth day with antithymocytic globulin (ATG). The transplanted uterus responded well to combined estrogen-progesterone therapy, with endometrial proliferation up to 18 mm. The patient had two episodes of withdrawal bleeding upon cessation of the hormonal therapy. Unfortunately, she developed acute vascular thrombosis 99 days after transplantation, and hysterectomy was necessary. Macro- and microscopic histopathological examination revealed acute thrombosis in the vessels of the uterine body, with resulting infarction. Both fallopian tubes remained viable, however, with no evidence of rejection. The acute vascular occlusion appeared to be caused by inadequate uterine structure support, which led to probable tension, torsion, or kinking of the connected vascular uterine grafts.

Cervical cancer

Select patients with early-stage cervical carcinoma may be eligible for conservative, fertility-preserving surgery [60]. The management of microinvasive lesions is based on the depth of invasion, and either cervical conization (for FIGO Stage IA_1) or radical trachelectomy with lymphadenectomy (for FIGO IA_1 with lymphovascular space involvement, FIGO IA_2, and FIGO IA adenocarcinoma) may be considered. Patients with FIGO Stage IB lesions less than 2 cm in size with limited endocervical involvement and no evidence of lymph node metastases, may also be candidates for radical trachelectomy. In patients who are selected for conservative therapy, there should be no clinical evidence of impaired fertility and a strong desire for future child-bearing. In addition, close surveillance should be instituted with scheduled Papanicoloau testing, colposcopic evaluation, and, for those patients treated by cervical conization, endocervical curettage.

Cervical conization

For women with Stage IA_1 squamous cell cervical cancer, because the rates of parametrial involvement and nodal metastases are negligible, cold-knife conization alone may be suitable under certain conditions (e.g., lack of LVSI, nulliparity, desirous of childbearing, etc.). Alternatively, laser CO_2 cervical conization under local anesthesia may be contemplated for microinvasive carcinoma, with a study of 62 patients by Diakomanolis *et al.* noting a 6.6% recurrence rate (CIN I only) over a mean follow-up period of 54 months [61]. The use of cervical conization in the management

3A

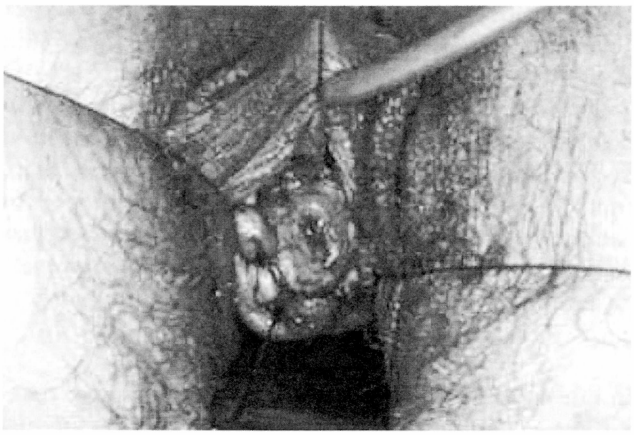
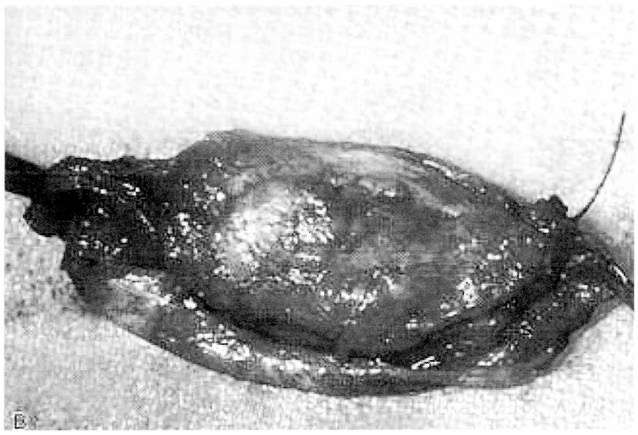


Fig. 3C



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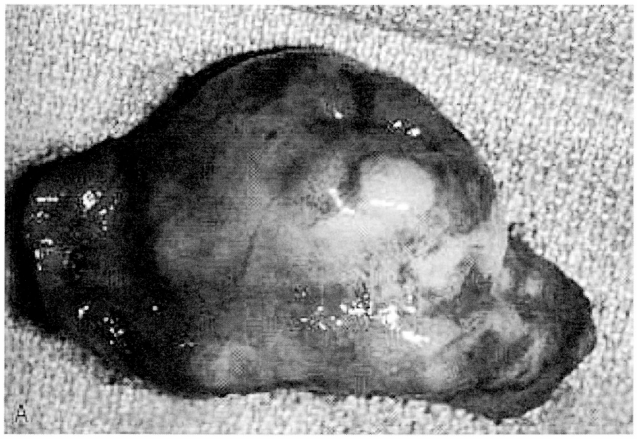

Fig. 3D

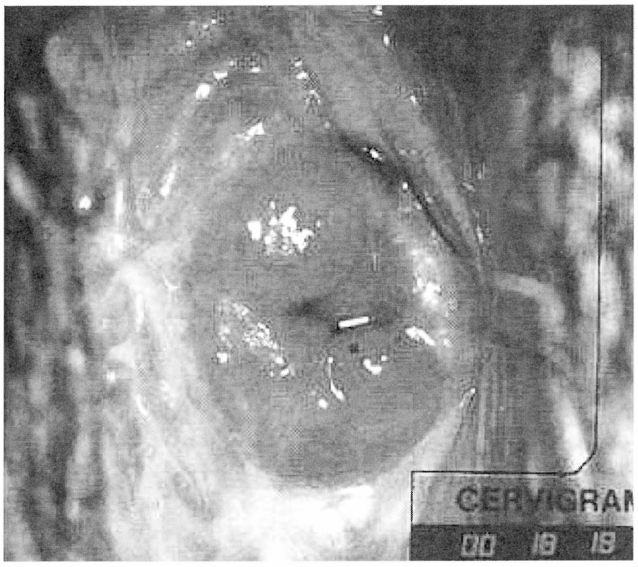

Figure 3. — Vaginal radical trachelectomy for early stage cervical carcinoma. All images from: Plante M.: "Fertility preservation in the management of gynecologic cancers". *Curr. Opin. Oncol.,* 2000, *12,* 497 (used with permission); 3A. — Aspect of the cervix immediately after completion of vaginal radical trachelectomy; 3B. — Ectocervical aspect showing the cervix and surrounding vaginal mucosa; 3C. — Endocervical aspect showing the proximal parametrium; 3D. — Residual cervix of a pregnant woman who had a vaginal radical trachelectomy procedure in the past. Aside from being shorter, the appearance of the cervix is essentially normal.

of "microinvasive" endocervical adenocarcinoma may also be an option for select women who wish to preserve fertility. McHale *et al.* explored the outcome on survival and fertility in women with cervical adenocarcinoma *in situ* and early invasive adenocarcioma treated conservatively between 1985 and 1996 [62]. Twenty of 41 women with adenocarcinoma in situ underwent cervical conization; of five patients with positive cone margins, two recurred and one developed an invasive adenocarcinoma at five years of follow-up. Four of 20 women with FIGO Stage IA lesions underwent cervical conization to preserve fertility, and three subsequently delivered healthy infants. None of these women developed recurrent disease after a median follow-up of 48 months. Schorge *et al.* prospectively employed the cervical conization technique to preserve fertility in five women with FIGO Stage IA adenocarcinoma of the uterine cervix [63]. None of the conization specimens revealed angiolymphatic space invasion and following six to 20 months of follow-up, none of the patients developed recurrent disease. One must always keep in mind that the primary objective is to clear the cancer with a satisfactory margin; all concerns regarding future pregnancy are secondary.

Vaginal radical trachelectomy

Patients with Stage IA_2 disease have a 6.3% risk of nodal metastases and therefore treatment must include a formal pelvic lymphadenectomy along with bilateral parametrectomy and upper vaginectomy. Thus, conization is not sufficient in these cases.

In the 1980s, Dargent designed a fertility-preserving operation for Stage IA_2 and some IB1 lesions [64]. A variant of the classical Shauta operation of vaginal radical hysterectomy, the vaginal radical trachelectomy (VRT) is always preceded by bilateral laparoscopic lymphadenectomies [65]. The VRT is performed with division of the uterus underneath

the isthmus, and at the completion of the procedure, the uterus is sutured to the vagina (Figure 3). Oncologically, the technique is satisfying as a wide margin around the lesion is obtained containing the parametria and the upper vagina, but leaving the body of the uterus *in situ* [66].

Intraoperative mandatory frozen section analysis should be performed on both the nodal tissue and the upper endocervical margins of the trachelectomy specimen. Upon a review of 61 VRT specimens, Tanguay *et al.* recommend a complementary radical hysterectomy when the tumor extends to within 5 mm of the margin [67]. These investigators also prefer a longitudinal rather than transverse frozen section when a macroscopic lesion is present as it permits measurement of the distance between the tumor and the endocervical margin.

Aggregate data from four centers (Dargent in France, n = 82 [68]; Covens *et al.* from Toronto, n = 58 [69]; Roy and Plante from Quebec n = 44 [70]; Shepherd *et al.* in the United Kingdom, n = 40 [71]) have documented a 3.1% (n = 7) recurrence rate among 224 patients, three of which were at distant sites (Table 3). The data reflecting obstetrical outcomes are quite encouraging and have been noteworthy for 96 pregnancies, of which 51 live births have resulted (Table 4). Covens *et al.* reported that all women in their series became pregnant within 12 months of attempting to conceive, giving a conception rate of 37% at one year [69]. Importantly most women were able to become pregnant without assisted reproductive technology. There have been 12 second trimester losses due to cervical weakness.

Table 3. — *Recurrence in a study of 224 patients who underwent radical vaginal trachelectomy with laparoscopic pelvic lymphadenectomy.*

Site of recurrence	No. of recurrence (%)
Parametrium	3 (1.3)
Pelvic sidewall	1 (0.4)
Distant	3 (1.3)*
Total	7 (3.1)

*Excludes two patients with small cell neuroendocrine tumors diagnosed on final pathology. Both patients died despite aggressive postoperative adjuvant chemotherapy.
Data drawn from Dargent and Mathevet [61], Dargent *et al.* [65], Covens *et al.* [66], Roy and Plante [67] and Shepherd *et al.* [68].
From: Stehman *et al.* Innovations in the treatment of invasive cervical cancer. *Cancer,* 2003, *98* (9 suppl.), 2052.

Bernardini *et al.* presented the obstetric outcomes of 80 patients from the Toronto group [72]. Thirty-nine patients attempted to conceive during a median follow-up period of 11 months, resulting in 22 pregnancies in 18 patients. Of the 22 pregnancies, 18 were viable, with 12 progressing to term and delivering by cesarean section. Preterm premature rupture of the membranes was the primary cause of preterm delivery. We currently recommend placement of a transabdominal cerclage over the mouth of the lower uterine segment with subsequent delivery of the neonate by cesarean section.

In an updated series of 72 cases and review of the literature the group from Quebec still maintain that the VRT is an oncologically safe procedure in well-selected patients with early stage disease [73]. Excluding a patient with a small cell neuroendocrine tumor who rapidly recurred and died, there were two recurrences (2.8%) and one death (1.4%) at a median follow-up of 60 months. The authors suggest that lesion size beyond 2 cm appears to be associated with a higher risk of recurrence. The first case of a centropelvic recurrence after radical trachelectomy appeared in 2004 in a patient who had been treated two years previously for a 2.1 cm lesion; minimal lymphatic space involvement was observed close to the tumor, and although 30 negative nodes were retrieved and all margins were free of disease, one margin measured only 5 mm [74]. Additionally, upon discovering a central pelvic recurrence of an endocervical adenocarcinoma seven years after VRT, Bali *et al.* have raised the question whether patients treated by VRT (in particular those with adenocarcinoma) should be offered hysterectomy once child-bearing has been accomplished [75].

Table 4. — *Obstetric results of a study of 224 patients who underwent radical vaginal trachelectomy with laparoscopic pelvic lymphadenectomy.*

Event		No. of events
Pregnancy		96 (n = 61 women)
Live birth		51 (includes preterm birth < 34 wks, n = 18)
First trimester loss		22
	Spontaneous abortion	16
	Therapeutic abortion	5
	Ectopic pregnancy	1
Second trimester loss		12
Current pregnancy		11

Data drawn from Dargent and Mathevet [61], Dargent *et al.* [65], Covens *et al.* [66], Roy and Plante [67] and Shepherd *et al.* [68].
From: Stehman *et al.* Innovations in the treatment of invasive cervical cancer. *Cancer,* 2003, *98* (9 suppl.), 2052.

By allowing for the preservation of the body of the uterus and thereby the potential for reproductive function, the VRT emerges as a true breakthrough in the management of young women with early-stage cervical cancer. VRT is currently the fertility-sparing procedure with the most available data supporting its use. Although these results are encouraging, there is lack of level I evidence (i.e., randomized controlled trials) comparing safety and survival rates between conservative and radical methods. Therefore, these techniques should be used by fully trained operators, with the understanding that it is not the standard treatment for this disease at present. In our opinion, the technique can be considered in conjunction with laparoscopic transperitoneal lymphadenectomy in the patient who strongly desires future fertility and harbors a Stage IA_1 lesion with LVSI, a IA_2 lesion or a IB1 tumor < 2 cm in diameter. Additional requirements include squamous cell histology when dealing with a clinical lesion, and limited endocervical involvement as determined by colposcopy and magnetic resonance imaging.

Abdominal radical trachelectomy

Potential benefits of the abdominal approach for radical trachelectomy include wider parametrial resection, possible lower intraoperative complication rates, and techniques familiar to most gynecologic oncologists [76]. Ungar *et al.* performed this procedure in 30 patients, ten with FIGO Stage IA_2 tumors, five with Stage IB_1 lesions, and five with Stage IB_2 [77]. During a median follow-up of 47 months, no recurrences have been detected. Among five women who attempted to conceive, three women have fallen pregnant resulting in one first trimester pregnancy loss and two cesarean section deliveries at term. Although this technique has not gained wide application, the authors contend that it appears to provide equivalent oncological safety to a standard Wertheim radical hysterectomy.

The performance of a satisfactory VRT can be technically complex when dealing with the proximal endocervical margins of an adenocarcinoma. We have moved away from the vaginal approach for glandular lesions, and exclusively perform the radical trachelectomy abdominally when confronted with an early-stage (i.e., FIGO IA) endocervical adenocarcinoma in patients desiring fertility preservation.

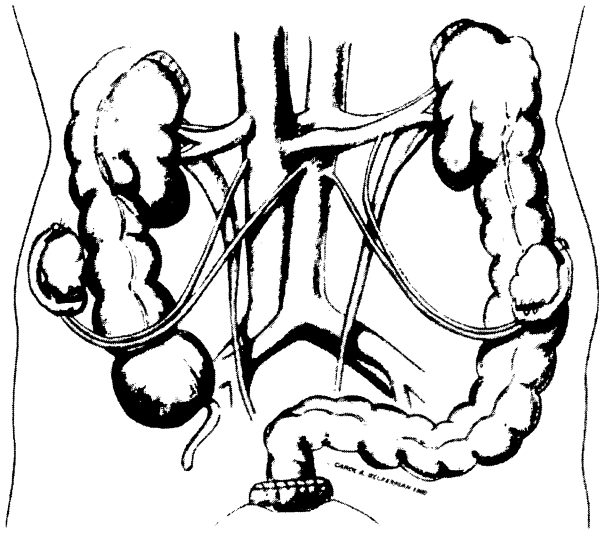

Figure 4. — Diagram illustrating the location of transposed adnexae to a nonpelvic site where they can be spared from postoperative pelvic irradiation. From: DiSaia P.J. Surgical aspects of cervical carcinoma. *Cancer,* 1981, *48,* 548 (used with permission).

Lateral ovarian transposition

Young patients with FIGO Stage I-IIA cervical carcinoma who are considered to be at high risk for requiring adjuvant pelvic irradiation (with or without radiosensitizing chemotherapy) should have the ovaries transposed to the paracolic gutters at the time of radical abdominal hysterectomy (Figure 4). The infundibulopelvic ligament is mobilized and two large metallic clips should be placed in an 'X' formation across the mesosalpinges to assist in radiographic localization during radiation treatment planning. Patients with locally advanced carcinomas (i.e., FIGO Stage IB_2-IVA) who will receive primary chemoirradiation can undergo lateral ovarian transposition via laparoscopy in anticipation of therapy.

The incidence of ovarian failure following transposition ranges from 28% to 50% when pelvic irradiation is used. There is a tendency to become postmenopausal if the scatter radiation dose at the transposed ovaries is > 300 cGy. This scatter radiation dose does not appear to depend on the distance the ovaries are placed from the linea innominata, The risk of premature ovarian failure when adjuvant radiation therapy is not required is approximately 5% in patients who have undergone lateral ovarian transposition. The risk of developing symptomatic ovarian cysts appears to be approximately 5%.

Husseinzadeh *et al.* performed lateral ovarian transposition in 22 patients with invasive cervical cancer, 15 of whom received whole pelvic external radiation therarpy [78]. Nine patients also received one or two intracavitary insertions. Ovarian function was measured by the serum gonadotropins, FSH, and LH. Five patients developed postmenopausal symptoms. Ovarian function was preserved in seven, all of whom received an average dose of 250 cGY to the ovaries via external radiation and intracavitary insertion(s). FSH values ranged from 3.3 to 38.8 mlU ml-1 (mean = 17.7 mlU ml-1).

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