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Fertility results after ovarian transposition for pelvic malignancies treated by external irradiation or brachytherapy

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The aim of this study was to assess the fertility outcome after ovarian transposition with uterine conservation and pelvic irradiation therapy for pelvic cancer. A total of 37 consecutive cases were reviewed. Of these, 27 patients were treated for a clear cell adenocarcinoma of the vagina and/or the cervix (group 1), nine for an ovarian pure dysgerminoma and one for a para-uterine soft tissue sarcoma (group 2). The pregnancy rate was 15% (4/27) in group 1 and 80% (8/10) in group 2 ($P = 0.01$). A total of 18 pregnancies was observed in 12 patients. Of these, 16 pregnancies were obtained spontaneously and two after in-vitro fertilization. Of the spontaneous pregnancies, 12 (75%) were observed with ovaries still in the abdominal cavity (not repositioned). These results show that the prognosis for fertility is excellent after ovarian transposition and irradiation in patients with morphologically normal genital tracts (group 2). The prognosis is not as good for patients treated for a clear cell adenocarcinoma of the vagina and/or the cervix who may have morphological and/or functional anomalies of the genital tract, following exposure to diethylstilboestrol and brachytherapy (group 1). Furthermore, these results show that repositioning of the ovary is not essential to achieve pregnancy.

Key words: fertility/ovarian transposition/pelvic cancer

Introduction

Ovarian transposition was proposed for the first time in 1958 to maintain ovarian function in patients irradiated for cervical cancer (McCall *et al.*, 1958). The results of this technique have been the subject of many studies into the hormonal function of the ovary (Bieler *et al.*, 1976; Hodel *et al.*, 1982; Husseinzadeh *et al.*, 1984; Ploch *et al.*, 1988; Anderson *et al.*, 1993). However, the other objective of ovarian transposition is to preserve fertility in patients where the uterus and at least one of the ovaries has been conserved. Recently other procedures, such as cryopreservation, grafting of ovarian tissue and oocyte freezing, were proposed in order to preserve ovarian function and fertility in patients treated by irradiation (Newton *et al.*, 1996). But ovarian transposition still has an important place in the preservation of ovarian function prior to irradiation. Analysis of the literature shows that very few studies have focused on the evaluation of fertility outcome following ovarian transposition. The aim of this study is to assess the fertility outcome following ovarian transposition, with uterine conservation and irradiation for pelvic cancer.

Material and methods

Patients

In the Institut Gustave Roussy from December 1974 to August 1994, 79 patients underwent ovarian transposition and uterine conservation with pelvic irradiation for pelvic cancer. Until 1993 ovarian transposition was performed by laparotomy (Michel *et al.*, 1983). Since 1993, this procedure was performed by laparoscopy (13 patients). When the ovaries were macroscopically normal both ovaries were transposed. For patients with an ovarian dysgerminoma, transposition of the non-affected ovary was performed. For the transposition the utero-ovarian ligament was ligated and cut and the Fallopian tube was separated from the ovary. The ureter was identified and the peritoneum incised along the infundibulo-pelvic ligament, in order to mobilize the ovaries. The ovaries were laterally transposed. In patients treated by laparotomy, the ovary was fixed to the peritoneum very high in paracolic gutters. In patients treated laparoscopically, the surgical procedure was performed using bipolar forceps and laparoscopic scissors. The ovary was fixed laterally. Two metal clips were applied to the transposed ovary for later X-ray localization. In the majority of cases, the transposed ovaries were outside of the external beam irradiation volume. In some cases, when the ovaries were included in this volume, we used a shield for the ovaries and digestive tract. Patients who underwent post-operative chemotherapy (patients suffering from lymphomas) were excluded from this study as such chemotherapy can affect ovarian function and in so doing alter assessments of fertility following combined radio-surgical therapy. Of these 79 patients, 42 (53%) were excluded: seven (9%) patients were lost to follow up, 14 (18%) died, 11 (14%) had radical surgery (hysterectomy) after the initial treatment for a recurrence, and 10 (12%) had a follow-up <2 years after a complete remission. Thirty-seven patients (47%) were followed up for a minimum of 2 years after a complete remission and two groups were defined based on histological type of the initial tumour (Table I). The mean age of these 37 patients was 20.7 years (SEM 2.8) (range 7–32) at the time of initial treatment.

Treatment of the patients in group 1 (patients with clear cell adenocarcinoma; CCA) was based on combined radio-surgical therapy (Gerbaulet *et al.*, 1989; Gerbaulet *et al.*, 1993). Patients first underwent surgery with complete exploration of the abdomen and pelvis, transposition of both ovaries and pelvic lymphadenectomy. If lymph nodes were free of metastasis, brachytherapy alone [60 grays (Gy)] was performed for small tumours. If the lymph nodes were metastatic and/or if the initial tumour was bulky, external irradiation (45 Gy) was delivered and boosted by brachytherapy (15 Gy).

For the patients in group 2 with a pure ovarian dysgerminoma, management included unilateral adnexectomy for a unilateral tumour,

Table I. Tumour type in 37 patients who underwent ovarian transposition of the non-affected ovary/ovaries

Tumour type	*n*
Group 1	
Clear cell adenocarcinoma of the vagina	27
Group 2	
Ovarian dysgerminoma	9
Pelvic soft tissue sarcoma	1
Total	37

Table II. Characteristics of 37 patients who underwent ovarian transposition

	Total	Group 1[a]	Group 2[a]
No. of patients	37	27	10
Mean ± SD age (years)	20.7 ± 5.7	19.6 ± 5.6	24 ± 5.1
Tumour stage[b]			
Stage I		10	9 (Ia[c])
Stage II		16	
Stage III		1	
Tumour stage[d]			T1
Treatment			
LOT	13	12	1
BT		20	
EBI			10
EBI+BT		7	
Mean ovarian dose (Gy)		2.2	1.9
(range)		(0.54–10)[e]	(0.5–3.4)[f]

[a]See Table I.
[b]Stage according to the FIGO classification.
[c]Stage for ovarian dysgerminoma.
[d]Patient with soft tissue sarcoma. TNM classification.
[e]Only one patient received 10 Gy. Certain patients in this group, with a small tumour and without nodal involvement, were treated with a utero-vaginal brachytherapy at 60 Gy (delivered on the uterine cervix and upper vagina).
LOT = laparoscopic ovarian transposition; BT = brachytherapy; EBI = external beam irradiation.

peritoneal cytology, transposition of the contralateral ovary and peritoneal biopsies. Patients with a stage Ia pure dysgerminoma underwent post-operative external irradiation of the iliac and para-aortic lymph nodes (25 or 35 Gy according to the lymph node status). Details concerning the patient's age, tumour stage, treatment and doses delivered to the ovaries are presented in Table II. Radiotherapy dosage to the ovaries was measured according to a procedure previously described (Haie-Meder *et al*., 1993).

Ovarian function and fertility results were assessed in these 37 patients. Ovarian function was monitored by a systematic post-operative ultrasonographic scan and assessment of gonadotrophins and oestradiol concentrations, 6 months after the transposition. This assessment was repeated when menstrual disorders and/or hot flushes were observed. Ovarian function was considered as normal when follicle stimulating hormone (FSH) concentration was <10 mIU/ml, oestradiol >50 pg/ml and when follicles were present on the ultrasound scan. Fertility was determined by recording the number of pregnancies, their evolution and the outcome of newborns.

Statistical analysis

The χ^2-test was used for statistical analysis, with statistical significance considered to be reached at $P < 0.05$ ($\chi^2 > 3.84$). The overall value of pregnancy rates and the median time elapsed between the end of tumour treatment and conception were determined.

Table III. Fertility outcomes in 37 patients who underwent ovarian transposition prior to irradiation for a pelvic tumour

	Total	Group 1[a]	Group 2[a]
No. of patients	37	27	10
Pregnant patients	12	4	8
Pregnancy rate (%)	32	15	80
Pregnancies	18	5	13
Miscarriages	5	4	1
Spontaneous pregnancy with abdominal ovary	12	3	9
Spontaneous pregnancy with repositioned ovary	4	3	1
Pregnancy obtained following in-vitro fertilization	2	1	1

[a]See Table I.

Results

No intra-operative or post-operative morbidity was observed in patients treated by laparotomy. One laparoscopic procedure was converted into a laparotomy because of bleeding during pelvic lymphadenectomy. In group 1 (27 cases), nine patients (33%) had menstrual disorders [amenorrhoea in five cases, unusually long (>50 days) interval between menstrual periods in four cases (oligomenorrhoea)]. Four patients with amenorrhoea had cervical stenosis. Menstruation started again after dilatation of the cervix. The other patient with amenorrhoea had uterine hypoplasia with normal ovarian function. In group 2, one patient had menstrual disorders (oligomenorrhoea) with normal biological tests (gonadotrophin and oestradiol levels). Her periods normalized a few months after the end of the irradiation. Within both groups, nine patients had ovarian cysts. These cysts were not suspected to be malignant on the ultrasound scan. Only one case required a percutaneous puncture and cytological examination, which confirmed the presence of a persistent luteal cyst. Medical treatment, used in all of the other cases, resulted in regression of the cysts.

A total of 18 pregnancies was obtained in 12 patients (12/37; 32%) (Table III). The overall pregnancy rate was 15% (4/27) in group 1 and 80% (8/10) in group 2 ($P = 0.01$). The overall pregnancy rate did not differ significantly between patients treated by laparoscopy or laparotomy [25% (3/13) versus 37% (9/24) respectively]. Of the 18 pregnancies, 12 (67%) were observed in nine patients whose ovaries were in the abdominal position, 16 (89%) were spontaneous and two following in-vitro fertilization (IVF). The median time elapsed between the end of tumour treatment and the beginning of the first pregnancy was 4.3 years (SEM 0.8) (range 2–7 years). Surgical repositioning of the ovaries was performed in three patients with persistent infertility. One of these patients had three pregnancies. Of the 18 pregnancies, five ended in a miscarriage (5/18; 28%) and 13 pregnancies produced 15 liveborn children (one patient had a premature delivery at 28 weeks gestation, with a healthy liveborn child). Of the five patients who had a miscarriage, four were from group 1. Among the 15 children born alive, one had a facial malformation which was considered to be unrelated to previous maternal history.

Discussion

The objective of ovarian transposition is to remove the ovaries from the area to be irradiated in order to preserve the ovarian function. The results of this transposition depend on the dose delivered to the ovaries and on the patient's age (Haie-Meder *et al*., 1993). The dose received by the ovaries, which can induce a complete menopause, ranges from 3.2 to 20 Gy (Lushbaugh and Casarett, 1976; Haie-Meder *et al*., 1993). The rate at which hormone function is preserved following ovarian transposition and pelvic irradiation for cervical cancer varies between 17 and 71% (Chambers *et al*., 1990; Anderson *et al*., 1993; Feeney *et al*., 1995). In our series, the dose received by the ovaries varied between 0.5 and 10 Gy and ovarian function was maintained in 100% of the patients following transposition and irradiation (Table II). This difference between our results and those found in the literature is attributable to age, which is the second major predictive factor in the maintenance of ovarian function following transposition (Lushbaugh and Casarett, 1976; Haie-Meder *et al*., 1993). A dose of 6 grays is sufficient to induce castration in patients aged $\geqslant$40 years whereas the ovaries can withstand 20 Gy in patients $<$20 years of age (Lushbaugh and Casarett, 1976). The average age of patients treated for a CCA or a pure ovarian dysgerminoma was lower than that of patients treated in other studies for cervical cancer. This accounts for the difference in the results concerning the preservation of ovarian function.

Menstrual disorders were far more frequent in patients in group 1 (33 versus 14%). Two reasons underlie this difference. The patients in group 1 were treated for CCA, following exposure to diethylstilboestrol (DES) in 60%. Such exposure leads to morphological and functional anomalies of the genital tract (uterine hypoplasia, cervical stenosis) which are likely to cause menstrual disorders (Herbst *et al*., 1981). Furthermore, these patients were treated by brachytherapy whereas the patients in group 2 received external irradiation alone. This utero-vaginal brachytherapy can also cause side-effects which can disturb menstrual function (endometrial atrophy, cervical stenosis).

The other objective of ovarian transposition is to maintain fertility in patients with uterine conservation. The few pregnancies which are described in the literature following ovarian transposition mainly concern patients treated for a lymphoma (Ray *et al*., 1970; Le Floch *et al*., 1976; Thomas *et al*., 1976). At present, such patients are excluded from this study as most of them are also treated with chemotherapy. Hence the reason why our team has ceased to perform ovarian transposition in these cases. In this series, 12 patients (32%) had 18 pregnancies. The rate of pregnancy is higher in group 2 (80% versus 15%; $P = 0.01$). This difference is easily explained. Patients in group 2 had a morphologically normal genital tract, whereas patients in group 1 had morphological and/or functional anomalies linked to exposure to DES (Herbst *et al*., 1981) or to the after-effects of utero-vaginal brachytherapy (endometrial atrophy, uterine sclerosis, cervical stenosis), all plausible explanations for their infertility. The rate of spontaneous miscarriages is also higher in patients who were exposed to DES (Herbst *et al*., 1981). In our series, 80% of miscarriages (4/5) occurred in patients in group 1. It should be pointed out that unilateral (patients in group 2) or bilateral (patients in group 1) transposition of the ovaries does not influence the rate of pregnancy (Haie-Meder *et al*., 1993).

Furthermore, of the 16 spontaneous pregnancies observed in this series, 12 were obtained with ovaries in the abdominal position (75%). These results show that the ovaries need not be repositioned to obtain a spontaneous pregnancy. Our team proposes repositioning of the ovary after 1 year of persistent infertility, when other factors associated with infertility have been ruled out. Finally, in spite of the irradiation of the ovaries, it should be underlined that no fetal morphological anomalies were observed in this series following irradiation.

In conclusion, in patients with a genital tract that appears to be morphologically normal, the ability to become pregnant and give birth following ovarian transposition and pelvic irradiation is preserved, with no increased risk of fetal malformation. In patients treated for CCA, associated genital abnormalities, due to DES exposure and/or brachytherapy, account for the low pregnancy rates observed following ovarian transposition. The ovary should not be automatically repositioned to obtain pregnancy. Repositioning should only be proposed when infertility persists.

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