Fertility sparing surgery for female cancer patients complementing cryotechniques

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Abstract

At present there are various strategies to protect fertility potential against the possibly harmful effects of cancer therapy. Options range from newly emerging pharmacological treatments (e.g. ovarian suppression, apoptotic inhibitors) to cryopreservation techniques (e.g. embryo, oocyte, ovarian tissue). Surgical interventions for cancer treatment may directly or indirectly harm future fertility potential. New developments in the surgery for tumours are affording different approaches to fertility-sparing options and these surgical approaches can be employed successfully in a large number of situations. This review investigates surgical treatments and its effect on future fertility for pre-malignant disease and cancer of the cervix, uterus and ovary as well as how it can compliment or replace the commonly used fertility preserving cryotechniques.

Key words: fertility sparing, fertility sparing surgery, cryopreservation.

Introduction

A significant number of young women are diagnosed annually with a malignancy during their childbearing years. Many patients are at risk of ovarian failure as a consequence of radiation therapy or treatment with cytotoxic chemotherapy. Surgery on the reproductive tract may also affect future fertility. At present there are various strategies to protect fertility potential against the possibly harmful effects of cancer therapy. The understanding of tumour biology, prognostic factors, epidemiology and behaviour at a microscopic and biochemical level improved tremendously over the years. Because of this better comprehension of cancer, there are more effective therapies to cure the disease but also to minimise problems associated with treatment. At present there are various strategies to protect fertility potential against the possibly harmful effects of cancer therapy. Options range from newly emerging pharmacological treatments (e.g. ovarian suppression, apoptotic inhibitors) to cryopreservation techniques (e.g. embryo, oocyte, ovarian tissue). Surgical interventions for cancer treatment may also directly or indirectly harm future fertility potential. New developments in the surgery for tumours are affording different approaches to fertility-sparing options and these surgical approaches can be employed successfully in a large number of situations.

The aim of this review is to investigate surgical treatments and its effect on future fertility for pre-malignant disease and cancer of the cervix, uterus and ovary as well as how it can compliment or replace the commonly used fertility preserving cryotechniques. Certain surgical aspects of other cancers will also be included.

Cervical precancer

According to the International Agency for Research on Cancer, cervical cancer accounts for nearly 10% of all new cancers diagnosed annually [1]. It is the second most common cancer in women and for every cancer diagnosed there are many more women who will have abnormal cervical cytology and a subsequent excisional treatment of the abnormality. Screening for cervical carcinoma in well-organized programmes has been shown to be effective in reducing the incidence and death rates due to the disease [2]. The intention of a cervical cytology screening programme is to detect pre-malignant lesions on the transformation zone of the cervix. Those patients with abnormal cytological results are then referred for further management.

In many clinics a "see-and-treat" approach is used and a patient with an abnormal smear often gets treatment at her first visit to the colposcopy clinic [3]. If the referral cytology indicates a high grade abnormality and the colposcopic picture fits with the cytology, a confirmatory biopsy of the cervix is not needed before excisional treatment is offered. One has to caution against blanket treatment of all patients purely on cytological results. Certain authors have shown that between 5 and 40% of all patients with abnormal cytology might not have histological abnormality on large loop excision of the transformation zone (LLETZ) cone biopsy [4]. It is therefore necessary to do a thorough colposcopic evaluation and to treat only those patients with a recognizable abnormality. If there is doubt about the severity of the abnormality, a biopsy should confirm a cervical intraepithelial neoplasia (CIN) II lesion or higher to justify treatment by destruction or resection of the transformation zone. Over-treatment may jeopardize a patient's future reproductive performance.

Reproductive outcome

Cervical intraepithelial neoplasia is most often diagnosed in women of reproductive years [5]. When treatment for a CIN lesion is considered, it would be prudent to take note of a patient's future reproductive wishes and to be aware of any adverse effects that cervical conization might have on her future fertility and obstetrical outcome. Cervical conization could theoretically have an adverse effect on a patient's fertility and lead to an increase in the incidence of miscarriage, premature rupture of membranes, premature labour, cervical distocia and precipitate labour.

Infertility

There is limited information about the effect of cervical conization on fertility. Buller found no evidence of secondary infertility in a group treated by cold knife conization [6]. Other authors did retrospective cohort studies on the effect of LLETZ conization on subsequent fertility and could also not show a decrease in pregnancy rate in the treatment groups compared to the cohorts [7-10]. In a prospective cohort study of patients treated by LLETZ, no deleterious effect on fertility could be demonstrated [11]. Kyrgiou in an excellent meta-analysis concluded: "...despite these difficulties, the available evidence suggests that fertility is not impaired after treatment for cervical intraepithelial neoplasia" [12].

These studies provide some reassurance that cervical conization is not a major cause of infertility. They unfortunately do not have sufficient power to exclude a subtle influence.

Cervical conization might lead to infertility by causing cervical stenosis or a decrease in the production of cervical mucus. Very rarely an ascending infection, caused by the conization, might lead to tubal damage. There have been case reports of women presenting with secondary infertility due to cervical stenosis and amucorrea post LLETZ [13]. Cervical stenosis seems to occur more often after cold knife cone biopsy than laser conization or LLETZ. With all modalities, a higher cone is associated with a greater occurrence of cervical stenosis [14, 15].

It is important to remember that the patient who presents with a CIN lesion, caused by sexually transmitted human papilloma virus (HPV) infection, is also at risk for tubal damage due to other sexually transmitted infections [6]. This will need to be taken into account when any conclusions regarding the effect of cervical conization on fertility are made.

Miscarriage

Cervical conization has not been shown to have any effect on the occurrence of first trimester miscarriages. Midtrimester miscarriages do seem to be significantly more common after cold knife conization. Moinian compared the pregnancies in a group of 414 patients before and after cold knife conization. It was found that late spontaneous miscarriages were seven times more frequent after cold knife conization than before [16]. This complication increases proportionately to the size of the cone biopsy [17].

Laser conization and LLETZ do not seem to cause an increase in the incidence of midtrimester miscarriages. This is possibly due to the smaller amount of cervical tissue removed by these methods when compared to cold knife conization. In a prospective study of 50 pregnancies in 86 patients treated by cold knife conization, LLETZ or laser conization, no late miscarriages were observed [14]. In a group of 54 women treated by laser conization, no late spontaneous abortions were documented in 71 pregnancies following conization [18]. Similarly, Althuisius found no second trimester abortions in 56 women delivering after LLETZ [19]. These studies were unfortunately not large enough to detect less overt effects of conization on the incidence of miscarriage. It would seem prudent to rather do a LLETZ or laser conization and only perform a cold knife conization if it is specifically indicated.

Preterm premature rupture of membranes and premature labour

In any study of the effect of cone biopsy on preterm premature rupture of membranes (PPROM) and preterm labour, it is important to bear in mind that CIN lesions have risk factors such as smoking, multiple sex partners and sexually transmitted infections in common with both PPROM and premature labour [20]. There are a number of mechanisms whereby a prior cone biopsy could lead to PPROM and preterm labour. The structural change in the cervix after a cone biopsy is important. The cervix might be shortened and the collagen formed in the scar tissue could be more fragile and react in a different manner from normal tissue to the hormonal changes of pregnancy. With the larger cones that remove endocervical glands also, the formation of cervical mucus may be impaired, thereby compromising the protective mucus plug and local immunological mechanisms. This might lead to ascending infections, the release of prostaglandins and PPROM or premature labour [20].

A group of 14 233 women of whom 170 had a cervical conization were studied for pregnancy outcome. Women who had cone biopsies for CIN lesions had a significantly increased risk of premature labour before 37 weeks when compared to the general population. This risk is increased *before* conization, but even *more so* after conization [20]. The authors postulate that the same risk factors that predispose patients to develop CIN lesions are also associated with premature labour, but that cervical conization has an additive effect.

Other earlier studies found cold knife and laser cervical conization to be associated with delivery before 37 weeks gestation [21-23]. There are, however, also a number of studies that found cold knife or laser conization and LLETZ *not* to be associated with preterm delivery or PPROM [6, 10, 14, 18, 24]. These initial conflicting results can possibly be explained by the generally small size of the study groups and the resultant lack of power to detect significant differences in the incidence of preterm birth.

Crane did a systematic review on the effect of LLETZ on subsequent pregnancy outcomes [25] and found LLETZ to be significantly associated with preterm birth before 37 weeks gestation. In a retrospective cohort study of 571 women who delivered after a LLETZ, the procedure was found to be associated with low birth weight, PPROM and preterm delivery before 37 weeks [26]. The increase in delivery before 34 weeks was not significant. In another report both laser conization and LLETZ were associated with a significant increased risk of PPROM and subsequent preterm delivery. This effect was more marked with increasing cone height [27].

In a large meta-analysis, there was a statistically significant association between cold knife conization and preterm delivery RR 2.59 (1.80-3.72) and low birth weight RR 2.53 (1.19-5.36) [12]. LLETZ was also statistically significant associated with preterm delivery RR 1.70 (1.24-2.35) and low birth weight RR 1.82 (1.09-3.06). Laser procedures, both ablation and conisation, were not associated with preterm delivery or low birth weight infants.

While it seems clear that cervical conization results in a greater risk of PPROM and preterm delivery and that this effect increases with increasing size of the cone, most women will have uncomplicated pregnancies following cervical conization. It remains to identify those at increased risk of having a complicated pregnancy after cervical conization. Cervical length on ultrasound of less than 25 mm is predictive of preterm birth in patients with prior cone biopsy [28]. It is unfortunately not yet clear how to best manage these patients. Prophylactic cerclage does not appear to prevent preterm labour in patients with prior cervical conization [29].

Precipitate labour and cervical distocia

Cervical conization disturbs the structural integrity of the cervix. The resultant scar tissue might not respond appropriately to the hormonal changes of parturition and result in an abnormal pattern of labour. It has been shown that neither precipitate nor prolonged labour is more common after cervical conization [21, 25]. There is, however, a small increase in the number of caesarean sections done for cervical distocia [16-18].

Cervical conization is an indispensable tool in the management of cervical intra-epithelial neoplasia but is not without risks. Cervical conization is associated with a small but significant increase in the incidence of PPROM and premature labour. The greater the amount of tissue removed by the cone, the greater is this effect. In isolated cases cervical conization might cause cervical stenosis and amucorrea which could lead to infertility.

Invasive cervical cancer

A significant number of women will be diagnosed with invasive cervical cancer before they have completed their families. Screening for cancer of the cervix results in a younger age at diagnosis but fortunately also often an earlier stage at diagnosis. Many women and their partners prefer to delay childbearing to first establish their careers and this may increase the risk for developing cancer when fertility is still very important. Factors affecting prognosis include the following:

Tumour volume

Tumour volume is one of the most important predictors of outcome in cervix cancer. Both adeno- and squamous carcinomas are staged according to the International Federation of Gynecology and Obstetrics (FIGO) classification and microscopic disease is staged according to tumour volume [30].

Lymphovascular space involvement

It is clear that lymph node involvement in cervical cancer conveys a poor prognosis for ultimate disease free survival. The number of cases with confirmed lymph node metastases decreases with decreasing stage. It would be ideal to identify those early cases with an increased risk for nodal involvement and a high risk for recurrence. Lymphatic- and/or vascular invasion by tumour indicate a higher risk for a poor prognosis [31].

Para-cervical or parametrial invasion

Not all tumours are surgically treatable and full surgical staging is not available in more advanced cases of cervical cancer. However in early operable disease parametrial invasion in surgical specimens is a significant poor prognostic factor for disease free survival and overall survival [32-34].

Lymph node metastases

Lymph node involvement in cervical cancer increases with increasing stage. Within stages, those with involved lymph nodes have a poorer prognosis and shorter disease free survival [35, 36]. Factors that influence lymph node involvement include tumour volume, lymphovascular space involvement, stage and parametrial involvement [36].

Resection margin status

Surgery as a single modality for cervical cancer treatment to safeguard fertility will only be successful if clear surgical margins can be guaranteed [37]. The accepted pathological tumour free margin is 3-5 mm [38, 39]. In cases where conservative surgery for fertility preservation is attempted, intra-operative frozen section to evaluate surgical margins is essential [40]. If, during uterus sparing surgery, the specimen is not clear at the resection margin as determined by frozen section, a further (deeper) resection should be done or a completion operation performed.

Treatment for stage Ia_2 to Ib_1 cervix cancer

The standard approach for treatment of slightly larger volume disease (FIGO stages Ia_2 to Ib_1) was until recently radical hysterectomy with pelvic lymph node dissection [41]. However, with radical hysterectomy (or pelvic radiotherapy) the patient was subsequently rendered infertile. Associated with radical surgery, there may be late neurological and rectal dysfunctions [42]. Some authors now argue that a simple hysterectomy, or even cone biopsy, with pelvic lymphadenectomy is adequate treatment [43, 44]. This approach afforded at least a 90% cure rate if lymph nodes were found negative during surgery.

The rational for less aggressive surgery

Less than 31% of all stage Ib_1 cases will have parametrial involvement [34]. It is also known that "positive parametrial involvement in stage Ia and Ib_1 cervical cancer is infrequent" [45]. In an attempt to predict those individuals who had parametrial involvement Bennedetti-Panici further found that parametrial involvement was found in less than 2% of cases if pelvic lymph nodes were negative [46]. Some authors have questioned the need of a complete parametrial excision in early cervical cancer [47]. A suitable approach intra-operatively may therefore be to do a frozen section of the pelvic lymph nodes before continuing with the radical hysterectomy and this approach can predict parametrial invasion with 90% sensitivity and 100% specificity. Those cases that were not accurately predicted had metastases less than 4 mm in diameter [46].

Treatment for stage Ia_1 cervix cancer

A small volume tumour, FIGO stage Ia_1, with depth of invasion of less than 3 mm and less than 7 mm on the surface, is adequately treated with a cold knife cone biopsy [41, 43, 44]. Laser conisation has also been reported as a safe option [48]. Care should be taken where lymphatic and or vascular invasion is present on initial biopsy when pelvic lymph adenectomy should be part of surgical management. It is important to consider excision margin status and the cone edges should be negative not only for invasive carcinoma but also for intra-epithelial disease. Ideally pathology should be reviewed at a multi-disciplinary team meeting and after treatment the patient should have careful cytology follow-up on a regular basis. Evaluation of the vulva and vagina is important when micro invasive cervical cancer is diagnosed because of the high incidence of multi-focal HPVs disease.

Even if stage 1a adenocarcinoma of the cervix is diagnosed during pregnancy, a conservative approach may be reasonable. A cone biopsy (also sometimes called a coin biopsy because of the flatter shape to avoid membrane rupture) during pregnancy with careful follow-up is acceptable as reported from Japan [49].

Dargent's operation (radical vaginal trachelectomy)

Dargent and other authors developed a radical operation for the treatment of early cervical tumours [50, 51]. This operation follows Halstead's principals but aims to preserve uterine function and makes conception, normal menstruation and even pregnancy possible. The removal of the cancer should include an adequate surgical margin and the resection includes parametrial tissue and pelvic lymph nodes. The aim of the operation is to include the complete cervix with a clear 1 cm margin beyond the tumour and a vaginal cuff and para-cervical tissues of approximately 2 cm.

Selection criteria for radical trachelectomy

Radical trachelectomy, whether it is done abdominally or trans-vaginally, should still be considered as a highly specialised procedure that should be performed in centres with the necessary surgical skill. When the decision is taken to be conservative in a patient with invasive cancer, oncological outcome should not be compromised in order to safeguard fertility. Only if the following criteria are met should a trachelectomy be offered [52]:

- carcinoma of the cervix,
- younger than 40 years of age with fertility desire,
- no unfavourable histology (e.g. neuro-endocrine tumours),
- stage Ia_1 with lymphovascular space invasion,
- stage Ia_2 or Ib_1 with tumours less than 2 cm,
- if the endocervix is involved with tumour, colposcopy (possibly with the aid of Kogan's endocervical speculum) or MRI is important to see the upper limit of the tumour, and
- no radiological evidence of lymph node- or systemic metastases.

Oncological features

The oncological outcome of trachelectomy procedures, as measured by tumour recurrences, compared very favourably with standard radical hysterectomy and is in the region of approximately 4% [53, 54]. Recurrences occurred up to eight years after the surgery, and although the recurrence rates are less than expected for a similar group of patients with stage Ib_1 disease, it may be because of the good prognostic small tumours that have been selected for this specific procedure. Despite the fact that the recurrence rates are very low, it is still very important that patients should have careful cytological, colposcopic and clinical follow-up on a regular basis.

Pregnancy outcomes for trachelectomy

In the general population, the average accepted fertility rate is in the region of about 85% [55]. Bernardini is of the opinion that the incidence of infertility, in a patient population suitable for conservative cervical cancer surgery, may be higher [56]. There is support for this opinion from Dargent [57] and Shepherd [58]. In an earlier report from Roy and Plante, none of the six patients trying to fall pregnant, could achieve a pregnancy [59]. Possible reasons for a decreased fertility rate in this population may include the fact that HPV infection is a marker of sexually transmitted infections. This could also indicate a population that is at higher risk for tubal damage due to previous upper genital tract infections. The trachelectomy procedure in itself may also compromise tubal function. If an open laparotomy is performed for the pelvic lymphadenectomy, manipulation of the uterus and other pelvic organs during surgery may cause adhesions.

Over the last decade, a few larger series have been published about pregnancy outcome in this patient population. The biggest risks for pregnancies after trachelectomy procedures are miscarriage, PPROM, early delivery and subsequent premature infants. This pregnancy loss occurs despite prophylactic cervical cerclage. In a review published during 2005 by Shepherd of a total of 406 cases, 171 pregnancies were reported which occurred in 118 women, resulting in 109 live births. Seventeen of the live born infants delivered before 32 weeks gestation [54]. Pregnancy loss before viability also is a serious concern. The number of first and second trimester losses from six different authors are summarised in Table I. It is clear that less than 60% of all deliveries occurred at term. Approximately 32% of pregnancies ended in loss and before viability. The first trimester losses may be similar to that of the general population, but the second trimester loss rate is much higher than expected.

Table I. Reported pregnancy loss rates from different units after trachelectomy

Author	Schaerth [60]	Burnett [61]	Shepherd [58]	Mathevet [14]	Bernardini [56]	Roy [59]	Total
First trimester loss [%]	0	0	29	16	14	16	13
Second trimester loss [%]	50	33	7	14	5	4	19
Delivery >37 weeks [%]	50	50	22	85	67	78	59

Bernardini speculates that the amount of cervical tissue remaining after trachelectomy may influence the incidence of PPROM [56]. The material used for the cervical cerclage may also make a clinical difference. A procedure called "Early Total Cervical Occlusion" (ETCO) has been suggested as a possible solution for PPROM [56, 62]. The specific factors causing premature rupture of membranes have been well studied, but there are no definitive conclusions. Both mechanical and infectious pathways may be involved in post-trachelectomy patients. The mucus plug, which may protect against infection, is usually absent if the patient has a short cervix. This absence of the mucus plug may lead to ascending infection [58]. The use of prophylactic antibiotics between 14 and 16 weeks, with regular bimonthly vaginal swabs for bacterial infections has been suggested as a possible management strategy [56]. Because of the higher rate of premature delivery, a single dose of corticosteroids, given routinely during the second trimester, may be a useful intervention [63]. In general obstetric literature regular sonographic evaluation for cervical incompetence has also been suggested as a possible early warning sign of premature birth [64, 65].

Neo-adjuvant chemotherapy followed by uterus conserving surgery

Plante described in 2006 three cases with locally advanced cervical cancer treated with neo-adjuvant chemotherapy (NACT) and radical vaginal trachelectomy [66]. All these patients were young, pre-menopausal patients who required future fertility. They were treated with:

- paclytaxol 175 mg per m^2 on day 1,
- cisplatinum 75 mg per m^2 on day 2,
- ifosphamide 5 g per m^2 over 24 h and
- mesna 5 g per m^2 on day 2 and 3.

These cycles are to be repeated every three weeks.

The chemotherapy was followed by laparoscopic pelvic lymph node dissection and radical vaginal trachelectomy. All cases had initial tumour sizes of less than 4 × 4 cm on MRI imaging. All patients had excellent pathological response on chemotherapy with negative nodes and surgical margins during surgery. However, the chemotherapy caused significant bone marrow suppression and there is also a concern about the use of ifosphamide and cisplatinum for ovarian follicle reserve. A successful pregnancy after treatment for invasive cervical cancer treated by NACT followed by conization has also been described [67]. Although NACT may make more patients suitable for uterus conserving surgery, it may reduce follicular reserve and cause premature ovarian failure.

Conservative surgery in endometrial cancer

Endometrial carcinoma is usually a disease of peri- or post-menopausal women. There are, however, a number of younger women who develop endometrial cancer, who usually present with excess estrogen associated with obesity, infertility and nulliparity. Overall, 2 to 14% of endometrial cancers occur in women younger than 40 years of age [68, 69]. There are many case reports in the literature of early stage, low-grade endometrial cancers that have been treated using uterus conserving therapies [70-73]. Hormonal treatment with progesterone, with or without additional gonadotropin releasing hormone analogue (GnRHa), often have the result that these early-stage tumours respond adequately to allow time for pregnancy. Surgery as part of conservative management of endometrial carcinoma or atypical endometrial hyperplasia has been described by Jadoul [69]. A small number of early-stage endometrial cancers were treated with partial hysteroscopic resection followed by GnRHa for 3 months. Regular endometrial curettage, combined with medroxy-progesterone acetate, has also been used for the treatment of early-stage tumours [74].

Despite the many case reports of successful conservative management, there remain some doubt about the safety of this approach. There have been isolated reports of metastatic disease in the myometrium or ovaries after conservative treatment [75, 76].

Fertility sparing surgery in ovarian cancer

Ovarian cancer is the sixth most common form of cancer in women but is the fourth leading cause of cancer death in the more developed regions of the world [1]. The symptoms are usually mild and the cancer is usually only diagnosed in advanced stages of the diseases. It occurs mainly in older women, but below the age of 40 years, the incidence can be as high as 3/100 000 women per year [77]. In these young women the question arises whether fertility sparing surgery is possible without compromising survival. Selected patients with Borderline Ovarian Tumours (BOTs) or early stage invasive epithelial cancer (FIGO stage Ia) with well differentiated tumours may be managed with fertility sparing surgery [77-82].

Successful pregnancies after conservative surgery for BOTs have been reported by various authors [77, 79, 80]. Selection criteria for conservative fertility-sparing management of BOTs depend on the risk for recurrence with invasive disease. The following factors may influence the risk for invasive disease:

- DNA ploidy status (aneuploid tumours had 19 times higher risk of dying of disease),
- stage at presentation,
- histological type (serous types have better outcome),
- age at diagnosis [83].

The presence of micro-invasion together with BOT has been seen as a possible poor prognostic indicator but a large meta analysis showed no increased risk for poor prognosis [84]. The World Health Organization (WHO) classification system states that, in borderline tumours, it is acceptable for stromal microinvasion up to 5 mm of measurement in any single focus or peritoneal implant [85]. Surgery for borderline tumours may include unilateral oophorectomy in patients with unilateral disease or an ovarian cystectomy with resection of all peritoneal and omental deposits in patients with bilateral disease. Careful surgical staging is important. After completion of the family, completion surgery with a total hysterectomy and a removal of any ovarian tissue is debatable. However, some authors suggest that late recurrences are reported in retrospective reports and therefore completion surgery is indicated [77].

Early stage, well-differentiated invasive epithelial ovarian carcinoma can also be treated successfully with fertility sparing surgery. In these patients accurate surgical staging is of the utmost importance. A surgical staging procedure should include peritoneal washings, removal of the primary tumour, multiple random peritoneal biopsies and infracolic omentectomy. A lymph node dissection may be considered in poorly differentiated tumours. Only if, after careful surgical staging, the patient remains a FIGO stage Ia can conservative management and omission of adjuvant therapy be safely advised.

Surgery for non-epithelial ovarian cancer should be individualized but fertility sparing surgery is a real option. Many of the germ cell and sex cord stromal tumours respond well to surgery alone or a combination of surgery and chemotherapy [86]. Individualization of care after final histological diagnosis will depend on the particular histological type.

Surgical ovarian trans-position

The human oocyte is exquisitely sensitive to the damaging effects of radiation and the estimated LD_{50} is less than 4 Gray [87]. A descriptive study by Wallace found that 37 out of 38 females had ovarian failure after whole abdominal irradiation of 20 to 30 Gray in childhood. 71% had primary amenorrhoea i.e. they never had normal pubertal development and premature menopause occurred in the rest with a median age of 23.5 years [88]. Ovarian trans-position outside the field of radiotherapy may reduce the dose to the ovary. Howell described how lateral trans-position of the ovaries to the para-colic gutters may reduce the radiotherapy dose by up to 95% [89]. This may protect the sensitive follicles from direct dose related damage. Other reports, however, were less optimistic and found that ovarian transposition may compromise blood supply and there was mixed success with this technique due to scattered radiation and vascular compromise [90]. Ovarian transposition may have a place in cases where the pelvic dose of radiotherapy is not high enough to be damaging to the other organs of the reproductive tract.

Cryopreservation of ovarian tissue

Recent reports describe transplantation of fresh ovarian tissue or complete ovaries to a location outside the field of radiotherapy. Animal studies demonstrated the potential for vascular anastomoses of ovaries in positions distant from the original [91]. Transplantation may be effective where large extended fields of radiotherapy may make transposition impossible. It will, however, not protect against toxic systemic chemotherapy.

Where transposition will be of no benefit due to systemic chemotherapy an option may be to remove ovarian tissue for the period of therapy, preserve the tissue and to replace ovarian tissue when toxic treatment is finished. Cryoprotection is successfully used for the preservation of sperm when men are treated with toxic chemotherapeutic regimes. The first live birth from cryopreserved ovarian tissue, which was re-implanted after sterilising cancer treatment, was recently reported from Belgium [92].

The obvious candidates for a technique like ovarian cryopreservation are young females with haematological cancer who need aggressive chemotherapy regimes. When bone marrow transplants are considered children often receive whole body irradiation with doses adequate to cause premature ovarian failure.

The histological examination of fresh and thawed ovarian tissue has been described and it should be part of routine practice to evaluate harvested tissue for the presence of microscopic metastases [93, 94]. If there is any doubt about possible reintroduction of carcinoma, it remains prudent not to store the tissue in the first instance. The risk for ovarian metastases from haematological malignancies in children is usually very low with the exception of leukaemia [94]. The risk for ovarian metastases from squamous cell carcinoma of the cervix is also very low [95, 96].

Oocyte cryopreservation and vitrification techniques are improving [97, 98] and the first succesful pregnancy was reported after removal of the ovary for BOT [99]. Despite the promise of oocyte preservation, the main concern still remains the time constraint before definitive cancer treatment can be given as adequate time is needed for controlled or hyperstimulation of the ovaries.

Conclusions

Young women who present with pre-malignant, borderline or invasive disease may qualify for conservative fertility sparing surgical treatment. The options for management should be decided after careful staging and discussion at multi disciplinary team meetings. The fertility wish of the patient should be taken into account and fertility sparing should be offered if it is a safe option.

If surgery is not appropriate treatment, cryopreservation of ovarian tissue or oocytes might still offer a solution.

References

1. www-dep.iarc.fr. Globocan 2002. Cited 2006, 28 May.
2. Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ 1999; 318: 904-8.
3. Lindeque BG. Management of cervical premalignant lesions. Best Pract Res Clin Obstet Gynaecol 2005; 19: 545-61.
4. Berek JS, Hacker NF. Practical Gynecologic Oncology. 3rd ed. Lippincot Williams & Wilkins 2000; 304.
5. Learmonth GM, Durcan CM, Beck JD. The changing incidence of cervical intra-epithelial neoplasia. S Afr Med J 1990; 77: 637-9.
6. Buller RE, Jones HW 3rd. Pregnancy following cervical conization. Am J Obstet Gynecol 1982; 142: 506-12.
7. Keijser KG, Kenemans P, van der Zanden PH, Schijf CP, Vooijs GP, Rolland R. Diathermy loop excision in the management of cervical intraepithelial neoplasia: diagnosis and treatment in one procedure. Am J Obstet Gynecol 1992; 166: 1281-7.
8. Turlington WT, Wright BD, Powell JL. Impact of the loop electrosurgical excision procedure on future fertility. J Reprod Med 1996; 41: 815-8.
9. Bigrigg A, Haffenden DK, Sheehan AL, Codling BW, Read MD. Efficacy and safety of large-loop excision of the transformation zone. Lancet 1994; 343: 32-4.
10. Cruickshank ME, Flannelly G, Campbell DM, Kitchener HC. Fertility and pregnancy outcome following large loop excision of the cervical transformation zone. Br J Obstet Gynaecol 1995; 102: 467-70.
11. Ferenczy A, Choukroun D, Falcone T, Franco E. The effect of cervical loop electrosurgical excision on subsequent pregnancy outcome: North American experience. Am J Obstet Gynecol 1995; 172: 1246-50.
12. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet 2006; 367: 489-98.
13. Kennedy S, Robinson J, Hallam N. LLETZ and infertility. Br J Obstet Gynaecol 1993; 100: 965.
14. Mathevet P, Chemali E, Roy M, Dargent D. Long-term outcome of a randomized study comparing three techniques of conization: cold knife, laser, and LEEP. Eur J Obstet Gynecol Reprod Biol 2003; 106: 214-8.
15. Baldauf JJ, Dreyfus M, Ritter J, Meyer P, Philippe E. Risk of cervical stenosis after large loop excision or laser conization. Obstet Gynecol 1996; 88: 933-8.
16. Moinian M, Andersch B. Does cervix conization increase the risk of complications in subsequent pregnancies? Acta Obstet Gynecol Scand 1982; 61: 101-3.
17. Leiman G, Harrison NA, Rubin A. Pregnancy following conization of the cervix: complications related to cone size. Am J Obstet Gynecol 1980; 136: 14-8.
18. Sagot P, Caroit Y, Winer N, Lopes P, Boog G. Obstetrical prognosis for carbon dioxide laser conisation of the uterine cervix. Eur J Obstet Gynecol Reprod Biol 1995; 58: 53-8.
19. Althuisius SM, Schornagel IJ, Dekker GA, van Geijn HP, Hummel P. Loop electrosurgical excision procedure of the cervix and time of delivery in subsequent pregnancy. Int J Gynaecol Obstet 2001; 72: 31-4.
20. Kristensen J, Langhoff-Roos J, Kristensen FB. Increased risk of preterm birth in women with cervical conization. Obstet Gynecol 1993; 81: 1005-8.
21. Jones JM, Sweetnam P, Hibbard BM. The outcome of pregnancy after cone biopsy of the cervix: a case-control study. Br J Obstet Gynaecol 1979; 86: 913-6.
22. Hagen B, Skjeldestad FE. The outcome of pregnancy after CO2 laser conisation of the cervix. Br J Obstet Gynaecol 1993; 100: 717-20.
23. Raio L, Ghezzi F, Di Naro E, Gomez R, Lüscher KP. Duration of pregnancy after carbon dioxide laser conization of the cervix: influence of cone height. Obstet Gynecol 1997; 90: 978-82.
24. Weber T, Obel EB. Pregnancy complications following conization of the uterine cervix (II). Acta Obstet Gynecol Scand 1979; 58: 347-51.
25. Crane JM. Pregnancy outcome after loop electrosurgical excision procedure: a systematic review. Obstet Gynecol 2003; 102: 1058-62.
26. Samson SL, Bentley JR, Fahey TJ, McKay DJ, Gill GH. The effect of loop electrosurgical excision procedure on future pregnancy outcome. Obstet Gynecol 2005; 105: 325-32.
27. Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. JAMA 2004; 291: 2100-6.
28. Berghella V, Pereira L, Gariepy A, Simonazzi G. Prior cone biopsy: prediction of preterm birth by cervical ultrasound. Am J Obstet Gynecol 2004; 191: 1393-7.

29. Zeisler H, Joura EA, Bancher-Todesca D, Hanzal E, Gitsch G. Prophylactic cerclage in pregnancy. Effect in women with a history of conization. J Reprod Med 1997; 42: 390-2.
30. http://www.figo.org/docs/staging_booklet.pdf. Cited 2008, 4 May.
31. Marchiolé P, Buénerd A, Benchaib M, Nezhat K, Dargent D, Mathevet P. Clinical significance of lympho vascular space involvement and lymph node micrometastases in early-stage cervical cancer: a retrospective case-control surgico-pathological study. Gynecol Oncol 2005; 97: 727-32.
32. Liu MT, Hsu JC, Liu WS, et al. Prognostic factors affecting the outcome of early cervical cancer treated with radical hysterectomy and post-operative adjuvant therapy. Eur J Cancer Care (Engl) 2008; 17: 174-81.
33. Metindir J, Bilir G. Prognostic factors affecting disease-free survival in early-stage cervical cancer patients undergoing radical hysterectomy and pelvic-paraaortic lymphadenectomy. Eur J Gynaecol Oncol 2007; 28: 28-32.
34. Benedetti-Panici P, Maneschi F, D'Andrea G, et al. Early cervical carcinoma: the natural history of lymph node involvement redefined on the basis of thorough parametrectomy and giant section study. Cancer 2000; 88: 2267-74.
35. Takeda N, Sakuragi N, Takeda M, et al. Multivariate analysis of histopathologic prognostic factors for invasive cervical cancer treated with radical hysterectomy and systematic retroperitoneal lymphadenectomy. Acta Obstet Gynecol Scand 2002; 81: 1144-51.
36. Rutledge TL, Kamelle SA, Tillmanns TD, et al. A comparison of stages IB1 and IB2 cervical cancers treated with radical hysterectomy. Is size the real difference? Gynecol Oncol 2004; 95: 70-6.
37. Bickford LR, Drezek RA, Yu TK. Intraoperative techniques and tumor margin status – room for improvement for cervical cancer patients of childbearing age. Gynecol Oncol 2007; 107 (1 Suppl 1): S180-6.
38. D'Arcy TJ, Roy A, Thomas A, McIndoe A, Soutter WP. Standards for the management of cervical and vulval carcinoma. BJOG 2000; 107: 846-8.
39. Estape RE, Angioli R, Madrigal M, et al. Close vaginal margins as a prognostic factor after radical hysterectomy. Gynecol Oncol 1998; 68: 229-32.
40. Tanguay C, Plante M, Renaud MC, Roy M, Tětu B. Vaginal radical trachelectomy in the treatment of cervical cancer: the role of frozen section. Int J Gynecol Pathol 2004; 23: 170-5.
41. Mota F. Microinvasive squamous carcinoma of the cervix: treatment modalities. Acta Obstet Gynecol Scand 2003; 82: 505-9.
42. Landoni F, Maneo A, Cormio G, et al. Class II versus class III radical hysterectomy in stage IB-IIA cervical cancer: a prospective randomized study. Gynecol Oncol 2001; 80: 3-12.
43. Gadducci A, Sartori E, Maggino T, et al. The clinical outcome of patients with stage Ia1 and Ia2 squamous cell carcinoma of the uterine cervix: a Cooperation Task Force (CTF) study. Eur J Gynaecol Oncol 2003; 24: 513-6.
44. Bisseling KC, Bekkers RL, Rome RM, Quinn MA. Treatment of microinvasive adenocarcinoma of the uterine cervix: a retrospective study and review of the literature. Gynecol Oncol 2007; 107: 424-30.
45. Steed H, Capstick V, Schepansky A, Honore L, Hiltz M, Faught W. Early cervical cancer and parametrial involvement: is it significant? Gynecol Oncol 2006; 103: 53-7.
46. Benedetti-Panici P, Palaia I, Basile S, et al. Conservative approaches in early stages of cervical cancer. Gynecol Oncol 2007; 107 (1 Suppl 1): S13-5.
47. Ungar L, Palfalvi L. Surgical treatment of lymph node metastases in stage IB cervical cancer: the laterally extended parametrectomy (LEP) procedure. Int J Gynecol Cancer 2003; 13: 647-51.
48. Ueda M, Ueki K, Kanemura M, et al. Conservative excisional laser conization for early invasive cervical cancer. Gynecol Oncol 2004; 95: 231-4.
49. Yahata T, Numata M, Kashima K, et al. Conservative treatment of stage IA1 adenocarcinoma of the cervix during pregnancy. Gynecol Oncol 2008; 109: 49-52.
50. Dargent D. Radical trachelectomy: an operation that preserves the fertility of young women with invasive cervical cancer. Bull Acad Natl Med 2001; 185: 1295-304; discussion 1305-6.
51. Dargent D, Mathevet P. Schauta's vaginal hysterectomy combined with laparoscopic lymphadenectomy. Baillieres Clin Obstet Gynaecol 1995; 9: 691-705.
52. Dursun P, LeBlanc E, Nogueira MC. Radical vaginal trachelectomy (Dargent's operation): a critical review of the literature. Eur J Surg Oncol 2007; 33: 933-41.
53. Maltaris T, Boehm D, Dittrich R, Seufert R, Koelbl H. Reproduction beyond cancer: a message of hope for young women. Gynecol Oncol 2006; 103: 1109-21.
54. Shepherd JH. Uterus-conserving surgery for invasive cervical cancer. Best Pract Res Clin Obstet Gynaecol 2005; 19: 577-90.
55. Zinaman MJ, Clegg ED, Brown CC, O'Connor J, Selevan SG. Estimates of human fertility and pregnancy loss. Fertil Steril 1996; 65: 503-9.
56. Bernardini M, Barrett J, Seaward G, Covens A. Pregnancy outcomes in patients after radical trachelectomy. Am J Obstet Gynecol 2003; 189: 1378-82.
57. Dargent D, Martin X, Sacchetoni A, Mathevet P. Laparoscopic vaginal radical trachelectomy: a treatment to preserve the fertility of cervical carcinoma patients. Cancer 2000; 88: 1877-82.
58. Shepherd JH, Mould T, Oram DH. Radical trachelectomy in early stage carcinoma of the cervix: outcome as judged by recurrence and fertility rates. BJOG 2001; 108: 882-5.
59. Roy M, Plante M. Pregnancies after radical vaginal trachelectomy for early-stage cervical cancer. Am J Obstet Gynecol 1998; 179: 1491-6.
60. Schlaerth JB, Spirtos NM, Schlaerth AC. Radical trachelectomy and pelvic lymphadenectomy with uterine preservation in the treatment of cervical cancer. Am J Obstet Gynecol 2003; 188: 29-34.
61. Burnett AF, Roman LD, O'Meara AT, Morrow CP. Radical vaginal trachelectomy and pelvic lymphadenectomy for preservation of fertility in early cervical carcinoma. Gynecol Oncol 2003; 88: 419-23.
62. Saling E. Prevention of habitual abortion and prematurity by early total occlusion of the external os uteri. Eur J Obstet Gynecol Reprod Biol 1984; 17: 65-70.
63. Murphy K, Aghajafari F, Hannah M. Antenatal corticosteroids for preterm birth. Semin Perinatol 2001; 25: 341-7.
64. Crane JM, Van den Hof M, Armson BA, Liston R. Transvaginal ultrasound in the prediction of preterm delivery: singleton and twin gestations. Obstet Gynecol 1997; 90: 357-63.
65. Iams JD, Johnson FF, Sonek J, Sachs L, Gebauer C, Samuels P. Cervical competence as a continuum: a study of ultrasonographic cervical length and obstetric performance. Am J Obstet Gynecol 1995; 172: 1097-103; discussion 1104-6.
66. Plante M, Lau S, Brydon L, Swenerton K, LeBlanc R, Roy M. Neoadjuvant chemotherapy followed by vaginal radical

trachelectomy in bulky stage IB1 cervical cancer: case report. Gynecol Oncol 2006; 101: 367-70.
67. Kobayashi Y, Akiyama F, Hasumi K. A case of successful pregnancy after treatment of invasive cervical cancer with systemic chemotherapy and conization. Gynecol Oncol 2006; 100: 213-5.
68. Wang CB, Wang CJ, Huang HJ, et al. Fertility-preserving treatment in young patients with endometrial adenocarcinoma. Cancer 2002; 94: 2192-8.
69. Jadoul P, Donnez J. Conservative treatment may be beneficial for young women with atypical endometrial hyperplasia or endometrial adenocarcinoma. Fertil Steril 2003; 80: 1315-24.
70. Kimmig R, Strowitzki T, Müller-Höcker J, Kürzl R, Korell M, Hepp H. Conservative treatment of endometrial cancer permitting subsequent triplet pregnancy. Gynecol Oncol 1995; 58: 255-7.
71. Lowe MP, Bender D, Sood AK, Davis W, Syrop CH, Sorosky JI. Two successful pregnancies after conservative treatment of endometrial cancer and assisted reproduction. Fertil Steril 2002; 77: 188-9.
72. Park JC, Cho CH, Rhee JH. A successful live birth through in vitro fertilization program after conservative treatment of FIGO grade I endometrial cancer. J Korean Med Sci 2006; 21: 567-71.
73. Pinto AB, Gopal M, Herzog TJ, Pfeifer JD, Williams DB. Successful in vitro fertilization pregnancy after conservative management of endometrial cancer. Fertil Steril 2001; 76: 826-9.
74. Niwa K, Tagami K, Lian Z, Onogi K, Mori H, Tamaya T. Outcome of fertility-preserving treatment in young women with endometrial carcinomas. BJOG 2005; 112: 317-20.
75. Huang SY, Jung SM, Ng KK, Chang YC, Lai CH. Ovarian metastasis in a nulliparous woman with endometrial adenocarcinoma failing conservative hormonal treatment. Gynecol Oncol 2005; 97: 652-5.
76. Hurst SA, Hartzfeld KM, Del Priore G. Occult myometrial recurrence after progesterone therapy to preserve fertility in a young patient with endometrial cancer. Fertil Steril 2008; 89: 724 e1-3.
77. Borgfeldt C, Iosif C, Måsbäck A. Fertility-sparing surgery and outcome in fertile women with ovarian borderline tumors and epithelial invasive ovarian cancer. Eur J Obstet Gynecol Reprod Biol 2007; 134: 110-4.
78. Cadron I, Leunen K, Van Gorp T, Amant F, Neven P, Vergote I. Management of borderline ovarian neoplasms. J Clin Oncol 2007; 25: 2928-37.
79. Seracchioli R, Venturoli S, Colombo FM, Govoni F, Missiroli S, Bagnoli A. Fertility and tumor recurrence rate after conservative laparoscopic management of young women with early-stage borderline ovarian tumors. Fertil Steril 2001; 76: 999-1004.
80. Swanton A, Bankhead CR, Kehoe S. Pregnancy rates after conservative treatment for borderline ovarian tumours: a systematic review. Eur J Obstet Gynecol Reprod Biol 2007; 135: 3-7.
81. Fauvet R, Poncelet C, Boccara J, Descamps P, Fondrinier E, Daraï E. Fertility after conservative treatment for borderline ovarian tumors: a French multicenter study. Fertil Steril 2005; 83: 284-90.
82. Suh-Burgmann E. Long-term outcomes following conservative surgery for borderline tumor of the ovary: a large population-based study. Gynecol Oncol 2006; 103: 841-7.
83. Kaern J, Trope CG, Kristensen GB, Abeler VM, Pettersen EO. DNA ploidy; the most important prognostic factor in patients with borderline tumors of the ovary. Int J Gynecol Cancer 1993; 3: 349-58.
84. Seidman JD, Kurman RJ. Ovarian serous borderline tumors: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol 2000; 31: 539-57.
85. Tavassoli FA, Devillee P. WHO Classification of Tumours: Pathology and Genetics of Tumours of the Breast and Female Genital Organs. WHO 2003.
86. Gershenson DM. Fertility-sparing surgery for malignancies in women. J Natl Cancer Inst Monogr 2005; (34): 43-7.
87. Wallace WH, Shalet SM, Hendry JH, Morris-Jones PH, Gattamaneni HR. Ovarian failure following abdominal irradiation in childhood: the radiosensitivity of the human oocyte. Br J Radiol 1989; 62: 995-8.
88. Wallace WH, Shalet SM, Crowne EC, Morris-Jones PH, Gattamaneni HR. Ovarian failure following abdominal irradiation in childhood: natural history and prognosis. Clin Oncol (R Coll Radiol) 1989; 1: 75-9.
89. Howell SJ, Shalet SM. Fertility preservation and management of gonadal failure associated with lymphoma therapy. Curr Oncol Rep 2002; 4: 443-52.
90. Husseinzadeh N, van Aken ML, Aron B. Ovarian transposition in young patients with invasive cervical cancer receiving radiation therapy. Int J Gynecol Cancer 1994; 4: 61-5.
91. Falcone T, Attaran M, Bedaiwy MA, Goldberg JM. Ovarian function preservation in the cancer patient. Fertil Steril 2004; 81: 243-57.
92. Donnez J, Dolmans MM, Demylle D, et al. Livebirth after orthotopic transplantation of cryopreserved ovarian tissue. Lancet 2004; 364: 1405-10.
93. Kim SS, Hwang IT, Lee HC. Heterotopic auto-transplantation of cryobanked human ovarian tissue as a strategy to restore ovarian function. Fertil Steril 2004; 82: 930-2.
94. Oktay K, Buyuk E. Ovarian transplantation in humans: indications, techniques and the risk of reseeding cancer. Eur J Obstet Gynecol Reprod Biol 2004; 113 Suppl 1: S45-7.
95. Nakanishi T, Wakai K, Ishikawa H, et al. A comparison of ovarian metastasis between squamous cell carcinoma and adenocarcinoma of the uterine cervix. Gynecol Oncol 2001; 82: 504-9.
96. Toki N, Tsukamoto N, Kaku T, et al. Microscopic ovarian metastasis of the uterine cervical cancer. Gynecol Oncol 1991; 41: 46-51.
97. Tao T, Del Valle A. Human oocyte and ovarian tissue cryopreservation and its application. J Assist Reprod Genet 2008; 25: 287-96.
98. Gardner DK, Sheehan CB, Rienzi L, Katz-Jaffe M, Larman MG. Analysis of oocyte physiology to improve cryopreservation procedures. Theriogenology 2007; 67: 64-72.
99. Porcu E, Venturoli S, Damiano G, et al. Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer. Reprod Biomed Online 2008; 17: 265-7.