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 amenorrhea 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 preterm 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 Ia2 to Ib1 cervix cancer

The standard approach for treatment of slightly larger volume disease (FIGO stages Ia2 to Ib1) 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 Ib1 cases will have parametrical involvement [34]. It is also known that “positive parametrical involvement in stage Ia and Ib1 cervical cancer is infrequent” [45]. In an attempt to predict those individuals who had parametrical involvement Bennedetti-Panici further found that parametrical 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 parametrical 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 parametrical 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 Ia1 cervix cancer

A small volume tumour, FIGO stage Ia1, 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].

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 1a, with lymphovascular space invasion,
- stage 1a or 1b, 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 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 1. 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.
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:

- paclitaxel 175 mg per m² on day 1,
- cisplatinum 75 mg per m² on day 2,
- ifosphamide 5 g per m² over 24 h and
- mesna 5 g per m² 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 medroxyprogesterone 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.

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

Fertility sparing surgery for female cancer patients complementing cryotechniques
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. Cryopreservation 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 re-introduction 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 successful 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 multidisciplinary 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.

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