Royal College of Obstetricians & Gynaecologists

Fertility Sparing Treatments in Gynaecological Cancers

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1. Introduction

The need to provide curative but less morbid treatments for patients with gynaecological malignancy has been appreciated over the past 20 years with a significant increase in the number of studies evaluating the potential risk and benefits of fertility sparing options. Generally, women are delaying conception. Annually in the UK, over 1000 women with cervical cancer, 120 with endometrial cancer and over 500 with ovarian cancer will present before the age of 45 years.[1]

2. Cervical cancer

2.1 Radical vaginal trachelectomy (RVT)

Although Aburel in Romania[2] initially presented the concept, popularisation of radical trachelectomy can be attributed to Daniel Dargent who published his first series in 1994.- The idea was to radically remove the cervix, upper vagina and para-cervical tissue vaginally, to remove the regional lymph nodes laparoscopically and to leave the body and fundus of the uterus in order to allow conception. A cerclage was placed in the neocervix in order to decrease the incidence of mid and late pregnancy loss. Since the initial cases, several studies have reported their outcomes in case series. Gien and Covens[4] and Rob et al.[5] summarised the data from all published series up to 2009 for over 700 cases and Lanowska[6] subsequently reported another series of 225 patients. In the combined series, 10–12% of patients required adjunctive treatment for positive margins, positive lymph nodes or poor prognostic features. The recurrence rate was 4.2–5.6% with a 5 year survival of 96.8–97.5%.

The majority of cases of cervical cancer have squamous cell carcinoma of the cervix and concern has been expressed about whether adenocarcinomas should be treated in the same way. As these tumours tend to arise higher in the endocervix they may not be suitable for local radical excision however the one study that looked specifically at this issue concluded that the position of the tumour rather than the histological type that is important and that RVT is a safe option in early adenocarcinoma of the cervix.[7]

A few studies have attempted to compare RVT with the more traditional radical hysterectomy and lymphadenectomy. These are summarised by Xu et al.[8] This summary revealed the recurrence rate to be 5.8% for radical vaginal trachelectomy versus 4.4% for radical hysterectomy, however there was no significant statistical difference. The 5 year survival in both groups was 97%.

A significantly raised recurrence rate has been observed with tumours over 2 cm in diameter;[9] most authors recommend restricting the use of RVT to those with smaller tumours.[10] This operation is not appropriate for those with metastatic disease.

Intraoperative and postoperative complication rates appear acceptable and similar to radical hysterectomy. Approximately 15% of RVT patients develop cervical stenosis4 and this can lead to dysmenorrhoea or infection.

2.2 Obstetric outcomes

Over 250 pregnancies which have resulted in over 100 live births have been reported up until 2009. Of those attempting to conceive, 41–79% were able to conceive. The rate of miscarriage in the 1st trimester was similar to the background population at 16–20% but there was an increase to 8–10% in the risk of 2nd trimester miscarriage. Only 70–75% of pregnancies delivered at term (> 37 weeks of gestation) but the risk of significant prematurity was only 12%.[4] In some series, attempts have been made to leave some endocervix[11] whilst others have tried Salings' operation (closure of the cervical os vaginally) to prevent ascending infection in an attempt to decrease the rate of pregnancy loss and prematurity.

2.3 Radical abdominal trachelectomy (RAT)

Although the majority of data available concern the operation of RVT, there are increasing reports of utilising the technique of radical abdominal trachelectomy. This operation is performed in the same manner as a radical hysterectomy, dissecting the parametrium in a way that is more familiar to gynaecological oncologists, and reproducing the removal of exactly the same paracervical tissue as a radical hysterectomy. The dissection can be performed through a laparotomy incision or laparoscopically. Whereas radical vaginal trachelectomy should be restricted to tumours less than 2 cm in diameter this technique may be especially useful in tumours larger than 2 cm that would otherwise be considered for a radical hysterectomy.

The combined data from the most recent two reports involved 94 women;[12,13] 3 recurrences, 2 deaths and 5/20 women successfully succeeded their attempt to conceive.

2.4 Neoadjuvant chemotherapy and cone biopsy

In an attempt to reduce morbidity and the radicality of surgery, some investigators have recommended the use of neoadjuvant chemotherapy followed by a simple cone biopsy and pelvic lymhadenectomy.[14–16] In the largest series of 21 patients there were no recurrences after a median follow up of 69 months.[15] During this follow up period, 6 patients conceived a total of 10 pregnancies. This option may be worth investigating further and might allow tumours above 2 cm to be treated in a way that allows a good prognosis. However, chemotherapy will have a damaging effect on ovarian function. Whether this is partial or complete will depend on the woman's pre-existing fertility status, the type of chemotherapy and the dose.

2.5 Cone biopsy alone

In microscopic tumours (stage 1A1) the incidence of metastatic nodal or parametrial disease is extremely small and therefore a simple cone biopsy has been used for cure for many years. Lymphadenectomy is not required[17–19] and fertility outcomes are excellent. Recent meta-analysis demonstrates that even in these cases there is an increased premature delivery rate[20] which is related to the proportion of the cervix that is removed[21] with delivery before 37 weeks of gestation in approximately 11% in comparison to 7% in untreated controls.[20] In a small series, conservative management of small volume stage 1B1 tumours has been reported by Naik et al.[22] Surgery in these cases included either cone biopsy or simple hysterectomy with pelvic lymph node dissection with good survival outcome. Of the 17 women treated this way, with a median follow up of 29 months, there were no reported cases of disease recurrence or death.

2.6 Ovarian transposition

If irradiating the pelvis becomes essential in the management of cervical cancer, for example, in the presence of pelvic nodal metastasis or parametrial invasion, ovarian transposition may be considered. Ovaries can be hitched up and sutured to the mid abdominal sidewall whilst their blood supply is preserved. They need to be transposed well above the level of the pelvic brim if they are to be excluded from the radiation field. This procedure may prevent early menopause and ovaries may be used at a later date for oocyte retrieval, in vitro fertilisation (IVF) and achieving pregnancy through surrogacy if appropriate.[23] However there is still a high risk of ovarian failure and oocyte retrieval should therefore be considered prior to administration of radiotherapy. This does not necessarily result in significant delay in treatment.

3. Endometrial cancer

The use of progestogen in the treatment of stage IA endometroid endometrial cancer without myometrial invasion is now well established although the numbers of patients requesting such treatment remains

small in any one institution. The published literature and highlights some of the issues (Appendix 1). A high proportion of the early endometrial cancers in young women are well differentiated and confined to the endometrium and many of the patients will have Polycystic Ovarian Syndrome. The diagnosis of endometrial carcinoma will frequently be made in the fertility clinic.

A major problem is that endometrial cancer is staged histopathologically at hysterectomy and without the uterus being removed other modalities have to be used to determine whether the tumour has invaded into the myometrium. MRI has a 90% accuracy[24] and is used in the majority of cases.

Various progestogenic regimens have been used with the most common being Medroxyprogesterone acetate 400–800 mg in divided daily doses or megestrol 160 mg daily. The levonorgestrol containing intrauterine system has been used in recent series and may be useful for maintenance therapy.

There is no consensus on the appropriate duration of treatment. Most authors have sampled the endometrium at 3 monthly intervals and the time to response varies between 3 and 12 months in all series.

3.1 Response rate

The response rate was 208/278 (75%) across all studies and there is no evidence that those who do not respond have a poorer prognosis than if they had proceeded to hysterectomy initially. The recurrence rate was high with 65/278 (23%) of women having recurring cancer at some time during the studies. Many of these women were successfully re-treated 3 or 4 times in order to allow them a window of opportunity to conceive.

There is also no consensus on long-term treatment. It is likely that a hysterectomy after childbearing will decrease the risk of long term disease and hormonal maintenance with the IUS, progestogen only pill or the combined oral contraceptive have been used in order to delay the hysterectomy.

Fertility rates tend to be lower in the population who develop endometrial cancer and most series have offered assisted conception immediately following complete response. A total of 89 live births have been recorded in the 278 women in these studies.[1] There is currently no evidence in the literature to suggest a difference in the pregnancy outcomes once conception has been achieved in this group of patients.

4. Epithelial ovarian cancer

Young women who present with epithelial ovarian cancer are a much more heterogenous group than those with either cervical or endometrial cancer. Although a number of series have been reported it is not known whether the histological subtype, breast cancer (BRCA) gene status or other factors influence the prognosis for these patients with early stage disease when treated conservatively.

It is recognised that in order to fully stage a patient with ovarian cancer a hysterectomy, removal of both ovaries, omentum, pelvic and para-aortic lymph nodes and collection of peritoneal washings and multiple random peritoneal biopsies are required.[25] There appears to be no additional benefit from taking a biopsy from a macroscopically normal contralateral ovary. Those who have confirmed stage I disease have a good prognosis. However if the uterus and the contralateral ovary are to be preserved there is presumably a risk that microscopic metastatic disease will not be recognised leading to an increased risk of recurrence. Bejamin et al.[26] addressed this issue by reporting 118 cases of early ovarian cancer that appeared to have disease confined to one ovary and were fully staged. In 3/118 (2.5%) the contralateral ovary had microscopic disease without spread elsewhere suggesting that if these patients had that ovary preserved they would have been at increased risk of recurrence.

A recent review[27] identified 9 studies with a total of 507 young women who underwent fertility sparing surgery for an early cancer of the ovary. They had a 10.3% chance of recurrence and 5.5% chance of death from disease, which is comparable to historical controls. A total of 186 full term deliveries were recorded in that population. Although their results are encouraging some series do show recurrent disease presenting confined to the preserved ovary in 4–6% of cases.[28,29]

The European Society of Gynecologic Oncology asked its fertility taskforce to make recommendations and these were published in 2011.[30] They concluded that Stage IA grade 1 and possibly grade 2 tumours of mucinous, endometrioid or serous types were suitable for fertility sparing surgery. Grade 1 stage IC could also be considered.

Recently published NICE guidelines have recommended that information and help should be made available to patients with ovarian cancer about fertility where appropriate.[31] These guidelines also reiterated the fact that if after modified staging, which would include complete staging as mentioned above but sparing the uterus and contralateral ovary, ovarian cancer appears to be contained in one ovary. Fertility sparing surgery may be offered to women who wish to consider this option.

5. Borderline ovarian tumours

Borderline tumours of the ovary occur more commonly in younger women and have frequently been treated with conservative surgery. The survival rates are 95–97% at 5 years, although recurrences tend to occur late and this can give a false sense of reassurance, as few studies have followed patients for 20–30 years.[32]

Two large studies involving 350 women initially demonstrated that conservative surgery resulted in a higher recurrence rate (16–19% versus 4.5–4.6%) in comparison to hysterectomy and removal of both ovaries, although the survival rates were comparable since the vast majority of patients with recurrence are salvaged[33,34] Two recent studies involving 184[35] and 155[36] women from South Korea have suggested there is no increase in recurrence rates with conservative surgery when compared to similar numbers of historical controls treated by radical surgery.

Certainly most gynaecological oncologists would offer conservative surgery in stage 1A disease but concern exists where disease has spread. For stage II or III disease the 5-year survival rates are 65–85%[35] and as these are slow growing tumours, many more patients will eventually succumb to disease over a longer follow up duration. Although fertility sparing surgery has been used in advanced cases there are no data to suggest this is safe and caution must be exercised.

6. Germ cell tumours

Radical surgery does not improve the outcome in germ cell tumours, which are usually particularly sensitive to chemotherapy.[36] The survival in advanced disease is still over 90% and the majority will resume normal menstrual function following their chemotherapy. They tend to occur mainly in very young adults and children and are uncommon so should be referred to specialist centres.

7. Storage of oocytes and embryos

Where fertility sparing surgery is not appropriate, it may occasionally be feasible to offer ovarian tissue retrieval and cryopreservation, ovarian stimulation and oocyte retrieval and/or IVF and embryo cryopreservation. Surrogacy will be required to achieve a pregnancy if the uterus is removed. Assisted conception techniques would usually be undertaken in the window between primary surgery and the start of chemotherapy or radiotherapy. A working partnership with a fertility clinic should be established so that rapid referral can be made and the patient seen expeditiously to avoid delay. In general, NHS funding of fertility preservation across the UK remains very dependent on local factors.

Oocyte cryopreservation is technically challenging and requires ovarian stimulation, with the resultant potential delay in cancer treatment. It may be contraindicated if the tumour is thought to be hormone sensitive although there are no scientific data on this. Oocyte vitrification may offer increased success rates in comparison with slow freezing, but is limited by the number of oocytes that can be obtained. This technique has been recommended by NICE fertility (draft) guidance[37] but only carries a 3–5% chance of resulting in a successful pregnancy per frozen egg. Embryo cryopreservation following IVF is

a routine procedure in fertility clinics; however, there are few data on its success rates in the context of fertility preservation in women with gynaecological cancers. Despite recent advances and improving success rates with oocyte and embryo preservation, there are no guarantees that these methods will result in a successful pregnancy for any individual. Ovarian tissue cryopreservation can be performed without significant delay but success rates from its use remain debatable.[38]

The field of ovarian tissue and oocyte retrieval and storage is fast changing and expert advice and help from fertility specialists needs to be sought in order to give the patient the best chance of future childbearing.

Despite these advances, a recent study showed that in USA only 4% of women treated for cancer take steps to preserve their fertility[39] with only 61% of women being counselled on the risk of cancer treatment to fertility by their oncology team despite receiving therapies that could reduce their fertility.[40] These studies did not include patients with gynaecological cancers and although gynaecologists are much more likely to be aware of fertility issues, clearly these figures could be improved upon.-

8. Opinion

Increasing knowledge of gynaecological cancers has enabled fertility sparing surgery to be offered to women who wish to preserve their childbearing ability. This should always be discussed with the patient in appropriate cases. Management of these women is complex and requires input from a multidisciplinary team, which should include experts with experience in managing these cases. Women involved need to be given ample information in order to make their decision as sometimes the balance between chances of compromising survival and preserving fertility is a fine one. The role of specialist gynaecological oncology nurses is invaluable in supporting the patients with their decision-making. Close working and discussion with fertility specialists is essential if women are to be given the best chance of achieving a successful pregnancy. Cancer centres treating women with gynaecological cancers should have the expertise and capacity to deal with the needs of women wishing to conserve their fertility or be able to refer the patients where this option is offered. Radical trachelectomy for cervical cancer has become a viable option for selected cases and gynaecological oncologists should be trained to acquire the skills required for this operation. Currently there is a lack of prospective data in the literature regarding outcome from many of these procedures discussed in this paper and more efforts should be focused in this direction.

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Appendix 1

Published literature regarding the treatment of grade 1 endometrial cancer

Author	Year	No. of Pts	Response (%)	Recurrence (%)	Live births	Regimen (mg)
Ramirez[41]	2004	81	62	15	20	36 MPA28 Megestrol
Niwa[42]	2005	12	12	8	6	MPA 400–600
Ota[43]	2005	12	5	2	3	MPA 600
Yang[44]	2005	6	4	2	2	Megestrol 160
Yamazawa[45]	2007	9	8	2	3	MPA 400
Ushijima[46]	2007	22	12	8	4	MPA 600
Signorelli[47]	2009	11	6	2	4	Cyclical progesterone
Eftekhar[48]	2009	21	18	3	5	Megestrol
Hahn[49]	2009	35	23	1	7	Megestrol 160
Minig[50]	2011	14	8	2	7	IUS + GnRH
Laurelli[51]	2011	14	13	1	1	Megestrol 160 + IUS
Park[52]	2011	14	13	4	9	MPA or Megestrol
Perri[53]	2011	27	24	15	17	Various
	Total	278	208 (75%)	65 (23%)	89	

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