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TOPIC HIGHLIGHT

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Impact of pelvic radiotherapy on the female genital tract and fertility preservation measures

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Abstract

Radiotherapy to the pelvis can have a major and deleterious impact on the female genital tract. Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy and social trends toward delayed childbirth many women treated for cervical cancer with radical chemo-radiotherapy will wish to attempt to preserve their fertility. Whilst there are now established and emerging techniques for preserving ovarian function and ovarian tissue, there remains the difficulty of the irradiated uterus which, even if pregnancy can be achieved, results in an increased risk for pregnancy-related complications. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

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Key words: Radiotherapy; Cervical carcinoma; Premature menopause; Infertility; Fertility preservation

Core tip: Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy many women treated for cervical cancer will wish to attempt to preserve their fertility. This article reviews emerging techniques for preserving ovarian function and ovarian tissue, as well as the impact on the uterus and the risk for pregnancy-related complications. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

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INTRODUCTION

Worldwide, cervical carcinoma is the third most common cancer in women, being responsible for nearly 10% of all cancers diagnosed in women in 2008[1]. However, there is major geographical variation in the incidence of cervical cancer across the globe, with a seven fold difference in the age-standardised incidence rate between East Africa, the region with the highest rate, and Western Asia, the region with the lowest rate[1]. Two peaks occur in the age-specific incidence rates of cervical carcinoma; the first peak occurs in women aged between 30-34 years and relates to women becoming sexually active in their late teens and early 1920s, resulting in an increase in the rate of infection with human papillomavirus[1,2]. In the United Kingdom between 2007 and 2009, the proportion

of cervical carcinoma cases occurring in women less than 45 years of age was 53%[1]. A continuous trend towards delayed childbearing has been observed in developed nations, resulting in an increase in the proportion of women diagnosed with a gynaecological cancer, typically cervical carcinoma, before their first pregnancy[3]. As a result of these epidemiological and social factors, a significant and perhaps increasing number of women of reproductive age who are diagnosed with a gynaecological cancer will wish to preserve their fertility[4-6].

The treatment of early-stage cervical carcinoma (International Federation of Gynecological Oncologists, FIGO stages Ⅰ and ⅡA cervical) is radical surgery, although radical radiotherapy is equally effective[7]. However, surgery for early-stage disease has the particular advantage of sparing fertility in cases that are suitable for radical trachelectomy[3]. For more advanced cases (FIGO stages ⅡB, Ⅲ and Ⅳ), standard treatment is with radical chemo-radiotherapy which combines external beam radiotherapy with weekly cisplatin followed by intra-uterine brachytherapy[8]. Radical radiotherapy for cervical carcinoma usually includes within the treatment volume: the pelvic lymph nodes, the uterus, the cervix and upper vagina, the fallopian tubes and ovaries, and the parametrial tissues. Modern radiotherapy techniques, utilising intensity-modulated external beam radiotherapy[9,10], and image-guided brachytherapy[11] can produce high rates of local control for cervical carcinoma. The prognosis for women with cervical carcinoma treated with radical chemo-radiotherapy varies according to FIGO stage, with the 5-year overall survival ranging from about 70% for stage ⅡB, to 50% for stages ⅢA and ⅢB, and 36% for stage ⅣA[12].

Given the favourable prognosis for many women treated for cervical carcinoma with radical chemo-radiotherapy, and given the demographic considerations discussed above, fertility preservation will often be an important issue for this cohort of women[4-6]. Unfortunately pelvic radiotherapy for pre-menopausal women, at radical treatment doses, results in complete ovarian failure and premature menopause. In addition, it causes direct damage to the uterus which in itself can result in an inability to conceive or carry a pregnancy to term[13,14]. The majority of the evidence for the effects of radiotherapy on female fertility derives from long-term follow-up studies of women treated with radiotherapy for cancer during childhood or adolescence[15-19]. Whilst this information from paediatric populations is of relevance to adult women receiving radiotherapy treatment, outcomes for patients treated in childhood are superior than for adults due to lower radiotherapy doses used for paediatric cancers and to the natural decline in fertility with age[20,21].

There are no completely satisfactory options for fertility preservation for women undergoing radical pelvic radiotherapy at present, yet there are interventions which should be offered for women to consider before they embark on treatment[4,22]. Evidence of the impact of pelvic radiotherapy on the female reproductive organs, the currently available fertility sparing options, and possible future strategies will be reviewed here.

IMPACT OF PELVIC RADIOTHERAPY ON THE FEMALE GENITAL TRACT

Pelvic radiotherapy by itself has significant consequences for female fertility. The degree of fertility impairment following radiotherapy is known to be dependent on the total radiation dose, the fractionation schedule, the radiation field, and age at the time of treatment[13,14]. It is now standard practice to give concurrent cisplatin chemotherapy as a radiosensitizer with radical radiotherapy for cervical carcinoma. It is reasonable to expect that this combination therapy will increase the impact of radiotherapy on fertility, on the basis of data on the long term effects of combined chemotherapy and radiotherapy in paediatric patients[23-25]. In addition, exposure to cisplatin in the context of single agent or multi-agent chemotherapy is known to cause ovarian failure, even in the absence of concomitant pelvic radiotherapy[13].

Aside from the impact of pelvic radiotherapy on the female reproductive organs, pelvic radiotherapy can also lead to damage to the vagina resulting in tissue fibrosis and vaginal stenosis. These late normal tissue changes can be severe and have a major impact on sexual function[26,27]. It is difficult to quantify these late effects of radiotherapy on vaginal tissues, and possibly as a result of such difficulties, the incidence of vaginal stenosis after radiotherapy reported in the literature ranges from 1.2% to 88%[26-29]. It is currently standard practice to attempt to minimise vaginal stenosis following pelvic radiotherapy by asking women to use vaginal dilators after radiotherapy[30-32]. A recent systematic review of evidence for the use of vaginal dilators following pelvic radiotherapy found that whilst vaginal dilation might help treat the late effects of radiotherapy, the use of vaginal dilation during treatment can cause increased tissue damage[29]. A Cochrane review by the same authors concluded that there is no reliable evidence to show that routine regular vaginal dilation during or after radiotherapy prevents the late effects of radiotherapy or improves quality of life[33].

Ovarian failure after radiotherapy

The human ovary contains a fixed number of primordial follicles, which is maximal during foetal life at 5 mo of gestation[5,18,20]. These are steadily lost through atresia, declining to about 500000 at the time of menarche[34]. After menarche, the number of viable primordial follicles continues to fall with increasing age, declining to about 1000 at the time of menopause at an average age of 50-51 years[20,35]. The rate of loss of ovarian follicles is not constant, and accelerated atresia of the primordial follicles occurs from approximately 35 years of age[35].

Oocytes are highly sensitive to radiation, and the LD50 (the radiation dose need to kill half the total number of oocytes) was estimated to be only 4 Gy[36], but more recently it has been reported to be less than 2 Gy[37]. Historically, complete ovarian failure has been known to occur after radiation doses in the region of 20 Gy in women under 40 years of age, and after only 6 Gy

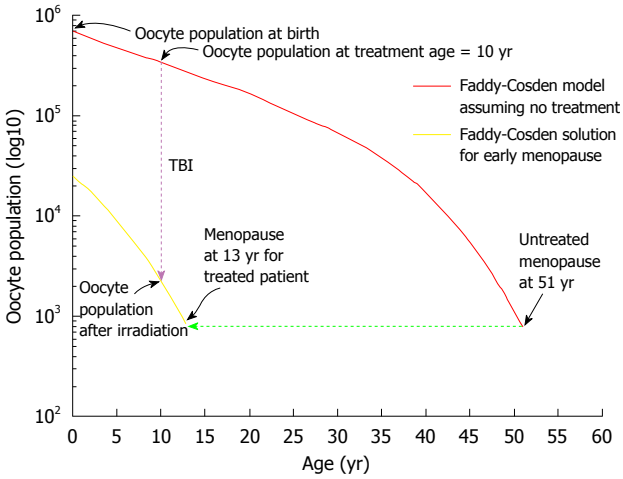

Figure 1 The effect of pelvic radiotherapy on oocyte population according to the Faddy-Gosden model. Faddy-Gosden model (Source[20], with permission) as extended by Wallace *et al*[21]. The graph illustrates the effect of total body irradiation with 14 Gy at 10 years, predicting ovarian failure at 13 years.

in older women[38]. Ovarian irradiation accelerates the natural process of follicular atresia, leading to premature menopause[20,21,37]. Due to the natural atresia of primordial follicles in the ovaries, for a given dose of radiation to the ovaries, the younger a woman is at the time of irradiation, the later will be the subsequent onset of premature menopause. This effect means that the sterilising dose of radiation falls with increasing age[20]. The Faddy-Gosden model of natural follicular atresia in healthy women has been extended by Wallace *et al*[20,21] to allow the prediction of the age of ovarian failure following treatment with a given dose of radiation (Figure 1). They have also calculated the effective sterilising radiotherapy doses (*i.e.*, the radiation dose causing ovarian failure in 97.5% of treated women) as a function of age: 20.3 Gy at birth, 18.4 Gy at 10 years, 16.5 Gy at 20 years, 14.3 Gy at 30 years and 9.5 Gy at 45 years[20].

Prediction of ovarian reserve prior to radiotherapy would be beneficial in order to avoid invasive procedures or unnecessary delays in treatment if fertility preserving measures are likely to be futile. Traditionally elevated follicle-stimulating hormone level has been used but various factors can cause a transient rise resulting in false prediction of menopause. Antimullerian hormone (AMH) is produced by growing follicles and may be a better indicator of ovarian function. The combination of serum AMH levels with ultrasound assessment of ovarian volume and total antral follicle count has been reported to more accurately predict the onset of ovarian failure[39,40].

Radiotherapy effects on the uterus

As well as the uterine dysfunction resulting from reduced ovarian hormone production, pelvic radiotherapy may also have a direct adverse effect on the uterus. Most of what is known about the long term effects of radiotherapy on the uterus comes from studies of women treated for childhood cancers[41,42]. However, these may be of limited relevance to adult women due to the significant changes that occur to the uterus during puberty[14,43,44]. Furthermore, the pre-pubertal uterus is thought to be more vulnerable to the effects of pelvic irradiation[14]. At puberty, as a result of rising ovarian oestrogen production, the uterus enlarges and changes shape from a tubular shaped organ to a pear shaped organ[43,44].

Radiotherapy doses between 14 and 30 Gy have been reported to result in adverse changes to the uterus including myometrial fibrosis, reduced uterine volume, reduced or undetectable blood supply and absent endometrium[41,42,45-47]. Critchley *et al*[41] assessed 10 women with premature ovarian failure due to whole abdominal irradiation in childhood. The uterine volume remained significantly lower in patients treated with pelvic radiotherapy compared with controls, and was correlated with age at the time of radiotherapy. Attempts to reverse these changes by means of cyclical hormone replacement therapy had limited success. Almost all treated women had loss of signal in one or both uterine arteries with Doppler ultrasound.

Holm *et al*[46] also used ultrasound to evaluate the impact of total body irradiation (TBI) with 8-14 Gy on internal genitalia and uterine blood flow. The median age was 12.7 years (range 6.1-17.6 years) at treatment and 21.5 years (range 11.6-25.6 years) at study entry. All participants had entered puberty but despite sufficient hormonal stimulus to achieve menarche in 11 out of 12 [eight with hormone replacement therapy (HRT) and 3 spontaneously], the median uterine volumes were still significantly reduced compared with normal controls. Uterine blood flow was impaired with systolic blood flow measurable in six of nine individuals, and diastolic blood flow visible in only one patient. These studies concluded that pre-pubertal irradiation may have an irreversible effect on uterine vasculature and development and that the endometrium may become unresponsive to hormonal stimuli due to a combination of effects on vasculature and to sex-steroid receptors[48].

The endometrial injury noted in the patients treated with TBI using a dose of 14.4 Gy was further studied by Bath *et al*[42] who propose this would prevent normal endometrial decidualisation (the post-ovulatory process of endometrial remodelling in preparation for pregnancy). This potentially leads to placental attachment disorders, including severe forms such as placenta accreta and placenta percreta[15,49,50]. In addition to these adverse endometrial changes it has also been suggested that pelvic radiotherapy can lead to thinning of the myometrium leading to an increased risk of uterine rupture during pregnancy[49,50].

There are few studies assessing the uterine changes after high dose pelvic radiotherapy in adults. Arrivé *et al*[51] undertook sequential magnetic resonance (MR) imaging imaging of 23 pre-menopausal women who received radiation for cervical cancer. A reduction in myometrial signal intensity on T2-weighted images was demonstrable by 1 mo after therapy and a decrease in uterine size was noted at 3 mo. A decrease in thickness and signal intensi-

ty of the endometrium was seen by 6 mo with earlier loss of uterine zonal anatomy. Four patients also had histopathological assessment which showed myometrial atrophy with fibrosis, inactive endometrium and reduction in vascular diameter. In postmenopausal women, irradiation did not significantly alter the MR imaging appearance of the uterus. The authors concluded that the early changes are due directly to radiotherapy but premature ovarian failure would have been contributory to the later atrophic changes.

Hormone replacement therapy is prescribed following radiotherapy to prevent menopausal symptoms. Combined cyclical therapy is indicated for patients previously treated for childhood cancers who still have a functional uterus. Following radiotherapy for cervical cancer, the very high doses delivered to the endometrial surface from brachytherapy is assumed to cause complete destruction of the basal layer of the endometrium. However, there have been several reports of persistent endometrial activity after treatment for cervical cancer. Habeshaw *et al*[52] reported 15 out of 63 patients treated for cervical cancer had breakthrough or cyclical vaginal bleeding when started on combined HRT several months to years after completing radiotherapy. Patients with an intact uterus following radiotherapy should therefore still be treated with oestrogen and a progestagen to avoid endometrial stimulation from unopposed oestrogen therapy.

Other than gestational surrogacy, there are no specific interventions available for uterine changes secondary to pelvic radiotherapy. Uterine dysfunction therefore represents a greater barrier to achieving viable pregnancy than does ovarian failure.

ADVERSE PREGNANCY OUTCOMES IN WOMEN TREATED WITH PELVIC RADIOTHERAPY

A number of long-term follow-up studies of pregnancy and neonatal outcomes in women treated in childhood for cancer with radiotherapy have now been published[17-19,53-57]. These studies have consistently found evidence of an increased risk of adverse pregnancy and neonatal outcomes for mothers with a prior history of irradiation in childhood, including: spontaneous miscarriages, pre-term labour, intrauterine growth retardation and low-birthweight infants[41,42,51,52]. While the risk increases with higher uterine dose, neonatal complications are noted with doses as low as 0.5 Gy.

There are no reports of a term pregnancy in patients who received more than 45 Gy to the whole uterus, which conventionally is the minimum dose delivered for gynaecological cancers. Hürmüz *et al*[58] have recently reported a patient with a full term pregnancy following pelvic chemoradiotherapy for anal cancer. Reviewing the radiotherapy fields, 30 Gy was delivered to the whole uterus while the lower segment and cervix received 50 Gy.

A fertility preserving approach using brachytherapy for cervical or vaginal clear cell adenocarcinoma was reviewed by Magné *et al*[59]. Seven of the 19 women treated for vaginal disease tried to become pregnant, with three delivering healthy term babies and one spontaneous abortion. In the 42 patients with cervical cancer, there were no successful pregnancies and two women reported spontaneous abortions.

A Canadian cohort study compared the risk of adverse pregnancy outcomes in female childhood cancer survivors who received abdominal-pelvic radiation and/or chemotherapy with alkylating agents with the risk among those who were treated by non-sterilising alkylating agents and those who were treated by non-sterilising surgery only[54]. There was no evidence of an increased risk of having a spontaneous abortion or an infant with a birth defect. Survivors receiving abdomino-pelvic radiotherapy were more likely to have a low birth weight infant (OR 3.64; 95%CI: 1.33-9.96), a premature low birth weight infant (OR 3.29; 95%CI: 0.97-11.1), or an infant who died in the perinatal period (OR 2.41; 95%CI: 0.50-11.5), compared with those receiving surgery. Risks of perinatal death and having a low birth weight infant increased with increasing dose of radiotherapy.

This association of children with low birth weight being born to mothers who had received pelvic radiotherapy has been confirmed in large studies from the United States that reviewed pregnancy outcomes among female participants in the Childhood Cancer Survivor Study (CCSS), a large multi-centre cohort of childhood cancer survivors[17,18,56]. The fertility of 5149 female survivors was compared to a cohort of 1441 randomly selected female siblings. The relative risk (RR) for survivors of ever being pregnant was 0.81 (95%CI: 0.73-0.90, $P < 0.001$) compared with siblings. In multivariate analysis, those who received an ovarian or uterine radiation dose greater than 5 Gy were less likely to have ever been pregnant with RR 0.56 for those receiving 5 to 10 Gy (95%CI: 0.37-0.85) and RR 0.18 for more than 10 Gy (95%CI: 0.13-0.26)[56].

Signorello *et al*[18] looked at singleton live births from female CCSS members from 1968 to 2002. This study included 2201 children of 1264 survivors and 1175 children of a comparison group of 601 female siblings. Survivors' children were more likely to be born pre-term than the siblings' children (21.1% *vs* 12.6%, $P < 0.001$). Compared with the children of survivors who did not receive radiotherapy, the children of survivors treated with a radiotherapy dose to the uterus of > 5 Gy had an increased risk of being born preterm (50.0% *vs* 19.6%, $P = 0.003$), low birth weight (36.2% *vs* 7.6%, $P = 0.001$), and small for gestational age (18.2% *vs* 7.8%, $P = 0.003$). Increased risks were also seen at lower uterine radiotherapy doses (starting at 0.5 Gy for preterm birth and at 2.5 Gy for low birth weight).

Similar findings were reported in a cohort review of 1688 female survivors of childhood cancer from the Danish Cancer Registry[57]. The outcomes of survivors, 2737 sisters, and 16700 comparison women in the population were identified from nationwide registries. More

than 34000 pregnancies were evaluated, 1479 of which were among cancer survivors. Survivors with any prior radiation had an increased excess risk of spontaneous abortion (OR 1.58; 95%CI: 1.2-2.2) which was greatest in those receiving higher doses to the ovaries and uterus (OR 2.8; 95%CI: 1.7-4.7).

The risk of radiotherapy induced germ line mutagenicity has also been assessed. In a United States cohort, 4214 children were born to cancer survivors with 157 (3.7%) having genetic diseases in contrast to 95 (4.1%) congenital conditions among 2339 children born to sibling controls. There was no increased risk of malformations, infant death, or altered sex ratio[55]. In the Danish series there were 82 (6.1%) birth defects among 1345 children of cancer survivors and 211 (5.0%) among 4225 children of sibling controls. These results provide reassurance that radiotherapy is very unlikely to cause inherited genetic disease in the children of cancer survivors[60].

These findings from large cohorts of women treated with abdomino-pelvic radiotherapy in childhood are all consistent with the complications of pregnancy that would be anticipated from the observations of reduced uterine volume, reduced elasticity of the myometrium and impaired uterine blood flow following pelvic radiotherapy described in section 2.2.

MEASURES TO PRESERVE FERTILITY PRIOR TO RADIOTHERAPY

Ovarian transposition

Whilst it may be practical to attempt to shield the ovaries from radiotherapy beams for some patients undergoing abdomino-pelvic radiotherapy, this will not be possible for women undergoing radical radiotherapy for gynaecological cancer due to proximity to the lymph node target volume. The ovaries are usually included in the radiation target volume for locally advanced cervical cancers due to the risk of ovarian metastases, with adenocarcinomas having a particular propensity for spread. However, for early stage disease and patients with pelvic sarcoma, lymphoma or receiving craniospinal irradiation there may be many benefits with ovarian preservation.

For these women, ovarian transposition, also known as oophoropexy, is a surgical procedure that attempts to move the ovaries outside of the radiation field. Although ovarian function can be preserved with this technique, it offers no protection to the uterus and so radiotherapy-induced uterine damage will continue to limit the chances of a successful pregnancy.

The procedure may be performed by open laparotomy and more recently with a laparoscopic technique[61-66]. The location selected for fixation of the transposed ovaries is dependent on the proposed pelvic radiotherapy field. For cervical carcinomas the transposed ovaries should be fixed well above the pelvic brim, since the standard superior border of the radiotherapy field is the L4/L5 or L3/4 vertebral space[66] (Figure 2). A high lateral position within the paracolic gutters is typically selected. Complications of ovarian transposition include benign ovarian cysts (23%), chronic pelvic pain (3%), and ovarian metastases (1%)[67]. Other reported complications include vascular injury, fallopian tube infarction, and ovarian migration[66-68].

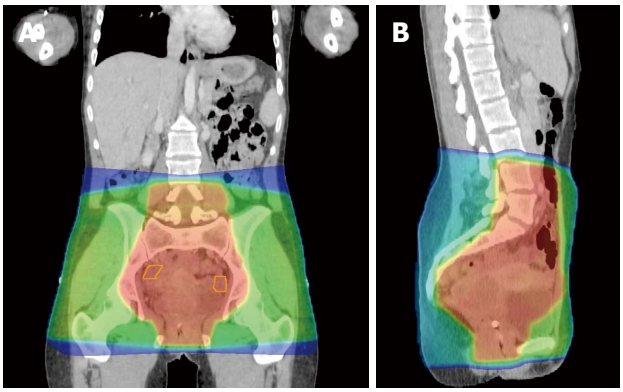

Figure 2 Typical radiotherapy dose distribution for cervical cancer. A: Coronal view; B: Sagittal view. The red area receives > 40 Gy, green > 10 Gy and blue < 10 Gy. Ovarian positions are contoured in yellow within the treated area, and transposition to the lateral para-colic region is required to be outside the low dose radiation region.

Covens *et al*[69] estimated the radiation exposure to each transposed ovary in three cervical cancer patients based on intra-uterine brachytherapy alone, and on external-beam pelvic radiotherapy (45 Gy), with and without para-aortic nodal irradiation (45 Gy). They estimated the mean radiation dose to each ovary following transposition for a course of intra-uterine brachytherapy as 1.3 Gy. The estimated doses for pelvic radiation without and with para-aortic lymph node irradiation were 1.4-1.9 Gy, and 2.3-3.1 Gy, respectively.

The reported success rates of ovarian transposition, in terms of preservation of ovarian function and fertility vary widely[15]. In a prospective study of 107 patients treated for cervical cancer, ovarian transposition to the paracolic gutters at the time of radical hysterectomy and lymphadenectomy was attempted[67]. Bilateral ovarian transposition was achieved in 104 of the 107 patients (98%). Of the 104 patients that underwent successful ovarian transposition, 59 were treated with vaginal brachytherapy alone to 60 Gy, and 25 other patients received external beam pelvic radiotherapy to 45 Gy with concurrent cisplatin, followed by vaginal brachytherapy to 15 Gy. Ovarian function was assessed by post-operative ultrasound and serial serum hormone levels. Preservation of ovarian function was achieved in 83% patients. After a median of 31 mo follow-up the rates of ovarian preservation were 100% for patients treated exclusively by surgery, 90% for patients treated by post-operative vaginal brachytherapy, and 60% for patients treated by post-operative external beam radiotherapy and vaginal brachytherapy.

Other methods of fertility preservation

The available methods for fertility preservation are summarised in Table 1. Aside from ovarian transposition, the

Table 1 Options for fertility preservation in women undergoing radical radiotherapy to the pelvis

Intervention	Procedure	Status	Time required	Pros	Cons
Ovarian transposition	Surgery to relocate ovaries within the abdomen outside of radiotherapy field	Established	Minimal (1 d)	Preserves oocytes and prevents premature menopause	Invasive surgical procedure; may require IVF; does nothing to protect uterus
Embryo cryopreservation	Mature oocyte aspiration, IVF, embryo freezing for later use	Established	2-3 wk	Established pregnancy rate of 20%-30% per transfer of 2 to 3 embryos	Requires 2 wk of ovarian stimulation; requires partner or donor sperm; requires functioning uterus or surrogacy
Donor oocytes and gestational surrogacy	IVF using donor oocytes and/or implantation of the embryo in a surrogate carrier	Established but infrequent	Not applicable	May be the only available option for some women with non-functioning uterus	Requires donor oocytes and gestational surrogate; ethical difficulties
Oocyte cryopreservation	Mature oocyte aspiration and freezing for later use	Experimental, live births reported, but only recommended as part of research	2-3 wk	Avoids need for partner or donor sperm at time of cryopreservation	Requires 2 wk of ovarian stimulation; requires functioning uterus or surrogacy
Ovarian tissue cryopreservation	Harvesting and freezing of ovarian tissue; re-implantation after radiotherapy or other gonadotoxic treatment	Experimental, but live births reported	Minimal (1 d)	Avoids need for partner or donor sperm at time of cryopreservation	Not appropriate if significant risk of ovarian involvement with malignancy

IVF: *In vitro* fertilisation.

only established method for women undergoing pelvic radiotherapy is embryo cryopreservation[5,6,70]. Mature oocytes are collected before treatment for *in-vitro* fertilisation and subsequent embryo cryopreservation. The Society for Assisted Reproductive Technology reported the live birth rate per transfer using frozen thawed embryos was 38.7% in United States women under 35 years old in 2010[71]. This technique requires a male partner or donor sperm for fertilisation. It may not suitable for many patients with cancer, because of the need for a period of ovarian stimulation that will delay the start of anti-cancer treatment.

Other fertility sparing interventions are available, but at the present time continue to be considered investigational. Oocyte cryopreservation requires ovarian stimulation and success depends on the number of mature oocytes retrieved. The oocyte survival rate (OR 2.46; 95%CI: 1.82-3.32) and high quality embryo rate (22% *vs* 8%) of oocyte cryopreservation with vitrification is significantly higher than with conventional slow freezing methods[72,73]. This improvement in technique and successful long term outcomes suggest this should now be considered an established treatment.

Ovarian tissue cryopreservation is the only option for prepubertal girls, patients who need treatment without delay or when ovarian stimulation is contraindicated due to hormone sensitive cancers[5,74-76]. Ovarian tissue is harvested laparoscopically and cryopreserved. With orthotopic transplantation, ovarian cortical fragments are reimplanted into the pelvic cavity once in remission[77,78]. However, following radiotherapy the vascular supply will be impaired and heterotopic transplantation to a remote site may be required. In 2001, Oktay *et al*[79] first reported successful transplantation to the forearm for a patient with cervical cancer, resulting in regular ovarian cycles for more than 1 year. There is the risk of introducing malignant cells preserved within the ovarian tissue. Since the first live birth was reported in 2004, orthotopic reimplantation has led to the birth of 17 healthy babies[80]. It also has the advantage of restoring endocrine function in young women after cancer treatment, with ovarian hormonal activity demonstrated within 3 to 6 mo after transplantation[81].

However, gestational surrogacy is the only option for women with preserved embryos, or preserved ovarian tissue but who have uterine compromise secondary to radiotherapy[76]. Similarly, women for whom other fertility sparing options are either inappropriate or fail have the option of oocyte donation with gestational surrogacy.

FUTURE PROSPECTS

Thankfully, fertility preservation is now an important consideration in oncology clinics, and the options available to patients are routinely offered. Despite the significant advances that have been made over the last three decades, and despite the availability of fertility sparing manoeuvres discussed above, there remain a significant number of women who will be rendered infertile as a result of life-saving cancer treatment. Techniques that do not require the preservation of embryos, or that do not require the delays associated with hormone stimulation, are the subject of ongoing intensive research efforts.

A particular problem remains for women whose uterus has been treated with radiotherapy. The first attempt at human uterus transplantation was undertaken in 2000. The transplanted uterus survived for 3 mo before failing due to thrombosis and necrosis[82]. This area has been the subject of ongoing active preclinical research efforts[83-86]. The first uterine transplant from a multi-organ donor was

undertaken in Turkey in 2011 and successfully achieved menstrual cycles after 20 d[87]. Recently two mother to daughter uterine transplants have been performed at the University of Gothenberg, Sweden and the results are awaited. Whilst there remain many technical obstacles to overcome, it may be possible to offer women who have received radiotherapy the option of uterus transplantation in the future.

CONCLUSION

Radiotherapy to the pelvis can have a major and deleterious impact on the female genital tract. Despite significant advances in the technical delivery of radical pelvic radiotherapy there remains no way to avoid delivering substantial radiation doses to the ovaries and uterus for patients undergoing treatment for gynaecological cancers. Due to improved cure rates from radical chemo-radiotherapy and social trends toward delayed childbirth many women treated for cervical cancer with radical chemo-radiotherapy will wish to attempt to preserve their fertility. Without specific interventions radical pelvic chemo-radiotherapy will always render women menopausal and infertile. Whilst there are now established and emerging techniques for preserving ovarian function and ovarian tissue, there remains the difficulty of the irradiated uterus which, even if pregnancy can be achieved, results in an increased risk for pregnancy-related complications, including spontaneous miscarriages, preterm labour, premature delivery, low birth weight, and placental abnormalities. Pre-menopausal women undergoing radical chemo-radiotherapy for gynaecological cancers need to be carefully counselled regarding the impact of this life-saving treatment on their fertility and sexual functioning, and offered support and access to such fertility sparing interventions as are currently available. Future developments may offer women in this difficult situation more and improved options for fertility preservation.

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